INTERNAL ANALGESIC TFM

Wednesday
November 16 1988

federal register

Part IV

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 310, 343, and 369

Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph; Notice of Proposed Rulemaking

4012 B1 - 25 - FDA - FR NOTICE 11-16-88

DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Parts 310, 343, and 369

[Docket No. 77N-0094]

Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the reports and recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products and the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and the public comments on the advance notices of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products and OTC menstrual drug products that were based on the Panels' respective recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by May 16, 1989. Because of the length and complexity of this proposed regulation, the agency is allowing a period of 180 days for comments and objections instead of the normal 60 days. New data by November 16, 1989. Comments on the new data by January 16, 1990. Written comments on the agency's economic impact determination by May 16, 1989.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the Federal Register of July 8, 1977 (42 FR 35346), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products, together with the recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by December 5, 1977. Reply comments in response to comments filed in the initial comment period could be submitted by February 6, 1978.

In a notice published in the Federal Register of March 21, 1980 (45 FR 18401), the agency advised that it had reopened the administrative record for OTC internal analgesic, antipyretic, and antirheumatic drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In the Federal Register of December 7, 1982 (47 FR 55076), FDA published an advance notice of proposed rulemaking to establish a monograph for OTC orally administered menstrual drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by March 7, 1983. Reply comments in response to comments filed in the initial comment period could be submitted by April 6, 1983.

In accordance with § 330.10(a)(10), the data and information considered by the Panels were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record for OTC internal analgesic, antipyretic, and antirheumatic drug products was reopened have also been put on display in the Dockets Management Branch.

In response to the advance notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products, two trade associations, several drug manufacturers, many health professionals, several consumers, a drug-standard-setting association, two health professional associations, a health foundation, and one consumer group submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

In response to the advance notice of proposed rulemaking for OTC menstrual drug products, the agency received two comments from drug manufacturers relevant to OTC internal analgesic drug products.

After reviewing and evaluating the Miscellaneous Internal Panel's recommendations regarding the use of OTC internal analgesic ingredients during the premenstrual and menstrual periods, the agency has determined that it is appropriate to include premenstrual and menstrual claims for these ingredients as part of the rulemaking for OTC internal analgesic drug products rather than to retain them as part of the rulemaking for OTC menstrual drug products and has transferred the comments relevant to those claims to this rulemaking. In this way, the various conditions for which an OTC internal analgesic drug product is safe and effective will be listed in one monograph. The agency's proposed regulation in the form of a tentative final monograph for OTC orally administered menstrual drug products is published elsewhere in this issue of the Federal Register.

In order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10), the present document is designated as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Part 343 (21 CFR Part 343) FDA states for the first time its position on the establishment of a monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products and the use of these products for premenstrual and menstrual symptoms. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products.

This proposal constitutes FDA's tentative adoption of the Internal Analgesic Panel's conclusions and recommendations on OTC internal analgesic, antipyretic, and antirheumatic drug products and the Miscellaneous Internal Panel's conclusions and recommendations on the use of OTC internal analgesic drug products for premenstrual and menstrual symptoms,

as modified on the basis of the comments received and the agency's independent evaluation of the Panels' reports. Modifications have been made for clarity and regulatory accuracy and to reflect any new information that has come to the agency's attention. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The Panel's conclusions and recommendations on the ingredient phenacetin are not addressed in this document. OTC drug products containing phenacetin are subject to the notice that FDA published on phenacetin in the Federal Register of October 5, 1983 (48 FR 45466), which requires removal of phenacetin from all prescription and OTC drug products (except for one prescription product on which a hearing request is pending).

The agency published an advance notice of proposed rulemaking on the reported association of the use of salicylates with Reye syndrome in the Federal Register of December 28, 1982 (47 FR 57886). Reye syndrome is a rare, acute, life-threatening condition, which primarily occurs in children or teenagers during the course of or while recovering from a mild respiratory tract infection, flu, chicken pox, or other viral illness. In the Federal Register of December 17, 1985 (50 FR 51400), the agency published a proposed rule to require the labeling of oral OTC aspirin and aspirin-containing drug products to bear a warning that such products should not be used to treat chicken pox or flu symptoms in children and teenagers before consulting a doctor about Reye syndrome. In addition to the warning statement, the agency proposed to prohibit OTC salicylate-containing drug products labeled solely for use by children (pediatric products) from recommending that the products be used in treating flu or chicken pox. The final rule was published in the Federal Register of March 7, 1986 (51 FR 8180). The final rule requires the labeling of orally or rectally administered OTC aspirin-containing drug products to prominently bear the following warning: "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome, a rare but serious illness." In addition, the regulation states that OTC drug products covered by the rule and labeled solely for use by children (pediatric products) shall not recommend the product for use in treating flu or chicken pox. This required warning statement and restriction on use of the drug were scheduled to expire June 6, 1988 unless extended by the agency through publication for notice and comment in the Federal Register. In the Federal Register of January 22, 1988 (53 FR 1796) the agency published a proposal to make the labeling provision permanent. A final rule was published in the Federal Register of June 9, 1988 (53 FR 21633), which expanded the required warning sratement to make clear that aspirin use in children and teenagers has been reported to be associated with Reye syndrome and made the labeling provision permanent. Therefore, the agency will incorporate the Reye syndrome warning into the final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products. The agency notes that one provision of the Reye syndrome labeling regulation, i.e., 21 CFR 201.314(h)(3) states that OTC drug products subject to the regulation and labeled solely for use by children (pediatric products) shall not recommend the product for use in treating flu or chicken pox. Because the Reye syndrome warning in § 201.314(h)(1) applies to both children and teenagers, and teenagers may use other than pediatric products, the agency is not proposing to include flu in the labeling indication for any oral OTC aspirin and aspirin-containing drug products. In addition, FDA noted in the final rule (53 FR 21635) that scentific research to date focuses on the association between Reye syndrome and aspirin, rather than on the broader category of drug products containing nonaspirin salicylates. FDA stated that it will consider extending the warning to nonaspirin salicylates if warranted by further research. Therefore, at this time the agency is not proposing to include flu in the labeling indication for any salicylate preparation. However, the agency is including "flu" in the indications allowed for products containing acetaminophen.

The agency is also aware of the National Institutes of Health (NIH) Consensus Development Conference on analgesic-associated kidney disease held February 27 to 29, 1984. The NIH Conference issued a statement concluding that considerable evidence indicates that combinations of antipyretic analgesics, taken in large doses over a long period of time, cause a specific form of kidney disease and chronic renal failure. Persons so exposed may be more susceptible to the subsequent development of uroepithelial tumors. The Conference also concluded that, in contrast, there is little evidence that preparations containing a single analgesic ingredient have been similarly abused and similarly harmful. The Conference recommended that serious consideration should be given to limiting OTC drug products to those containing a single antipyretic-analgesic agent. The agency advises that the final Conference report is being included in this administrative record (see OTC volume 03BTFM), which has now been reopened with publication of this tentative final monograph. The agency invites specific comment on this issue and will address the Conference's recommendations in the final rule.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate

commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products (published in the Federal Register of July 8, 1977 (42 FR 35346)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the Federal Register and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the Federal Register. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the Federal Register of July 21, 1972 (37 FR 14633) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

I. The Agency's Tentative Conclusions on the Comments and Reply Comments

A. General Comments

1. Several comments contended that OTC drug monographs are interpretative, as opposed to substantive, regulations.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the Federal Register of May 11, 1972 (37 FR 9464), and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the Federal Register of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association v. Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers v. FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).

2. One comment stated that FDA should provide better physician education on the treatment of drug toxicity, as well as on the potential toxicity of medications currently on the market. Other comments suggested that an educational program should be jointly initiated by FDA, the pharmaceutical industry, and the medical and pharmacy professions to better educate consumers on the appropriate use of analgesic products, e.g., the use of aspirin during pregnancy.

The agency supports and is actively engaged in educational programs for consumers, physicians, and health professionals. One way in which FDA provides information on drug interactions, toxicities, and other pertinent topics is through the "FDA Drug Bulletin." This publication is routinely mailed to physicians and other health professionals. One issue, for example, was devoted to alcohol-drug interactions, including possible interactions of alcohol with aspirin, other salicylates, and acetaminophen (Ref. 1). Another issue, which discussed the use of aspirin in patients with a previous myocardial infarction or unstable angina pectoris, included a discussion of adverse reactions that occurred from the doses of aspirin used in the studies (Ref. 2).

FDA also has consumer education programs on human drugs. Each program is implemented by FDA consumer affairs officers who provide health-related information, through talks, films, or slides, to diverse groups of people, such as health professionals, parents, teachers, and others. These groups, in turn, often help to disseminate the information further. The consumer education programs on human drugs consist of subprograms such as "Drugs and Pregnancy" and "Safe and Effective Use of Drugs," which include publications that provide information on the use of OTC internal analgesic drug products among others. Additional agency publications are also available to consumers. For example, "FDA Consumer" and "FDA Consumer Memo" have contained articles on drugs and pregnancy and the uses and dangers of OTC drugs that relieve pain (Refs. 3 through 6).

As new information becomes available, FDA updates these programs to assure continuing education of both consumers and health professionals. In addition, the agency participates in cooperative private-public programs through such organizations as the National Council on Patient Information and Education, which involves industry, health professionals, and consumers in a variety of education and information programs.

References

(1) Food and Drug Administration, "FDA Drug Bulletin," Vol. 9, No. 2, June 1979.

(2) Food and Drug Administration, "FDA Drug Bulletin," Vol. 15, No. 4, December 1985.

(3) Postotnik, P., "Drugs and Pregnancy," *FDA Consumer*, 12:6–10, 1978.

(4) Hecht, A., "Painkillers: Their Uses and Dangers," *FDA Consumer*, 2:6–11, 1977.

(5) Food and Drug Administration, "Nonprescription Pain Relievers," *FDA Consumer Memo*, HEW Publication No. (FDA) 78–3078.

(6) Food and Drug Administration, "Self-Medication," *FDA Consumer Memo*, HEW Publication No. (FDA) 73–3025.

3. One comment urged that future OTC drug monograph documents of more than 10 pages include a table of contents, an index, and boldface headings throughout the text for ease of

reading and locating information in the text.

In publishing documents in the Federal Register, FDA follows guidelines established by the National Archives and the Office of the Federal Register in an effort to make all government documents consistent in format and style.

Since the comment was written, Federal Register format has changed. The new format now includes headings in bold and italic type which make it easier to read and locate information in OTC Panel reports, tentative final monographs, and final monographs. However, no provision has been made for including either tables of contents or indexes in documents published in the Federal Register.

4. Two comments stated that neither a gastroenterologist nor a hematologist served on the Panel and that the expertise of such specialists was essential to the development of the Panel's report. Several other comments questioned the scientific validity of the Panel's report. These comments argued that the Panel frequently misinterpreted information and data to support its conclusions, reached conclusions contrary to the data submitted or testimony presented to it, and relied too heavily on references that are secondary, out-of-date, and unavailable to the scientific community (i.e., not published in scientific journals).

The agency points out that, although the Internal Analgesic Panel did not include a gastroenterologist or a hematologist, experts in the fields of gastroenterology and hematology appeared before the Panel to express their views and present data for the Panel's consideration. Thus, the Panel was not denied expertise in these areas in developing its report.

In evaluating the scientific validity of the Panel's report, the agency has considered the views expressed in the comments, reviewed current scientific literature, and consulted experts outside the agency when necessary. All data on which the Panel based its conclusions, including published and unpublished references, are available to interested persons, including the scientific community, through the Dockets Management Branch (address above).

5. Two comments believed that the Panel recommended changing the marketing status of aspirin products from OTC to prescription only. The comments opposed such a change and expressed concern that making aspirin products available by prescription only would limit consumers' access to these products and would greatly increase their cost. A third comment asserted that aspirin should be available only by prescription, but gave no reasons.

The Panel found aspirin to be safe and effective for OTC use as an analgesic and antipyretic and did not recommend making aspirin products available only by prescription. The agency agrees with this conclusion and emphasizes that aspirin products will continue to be available OTC.

6. One comment stated that the Panel should have deferred caffeine, as it deferred other ingredients in its report (42 FR 35350), to the Advisory Review Panel on OTC Sedative, Sleep-Aid, and Tranquilizer Drug Products (Sleep-Aid Panel) "for uses other than an analgesic adjuvant."

The Internal Analgesic Panel reviewed submissions for caffeine-containing analgesic products that were labeled as analgesics or as analgesic-stimulants. The Panel reviewed caffeine for its safety and effectiveness as an analgesic and as an analgesic adjuvant, but not as a stimulant because stimulant use was reviewed by the Sleep-Aid Panel in its report published in the Federal Register of December 8, 1975 (40 FR 57292). The agency presented its tentative conclusions on caffeine in the OTC nighttime sleep-aid and stimulant products notice of proposed rulemaking in the Federal Register of June 13, 1978 (43 FR 25544). In the Federal Register of February 29, 1988 (53 FR 6100), the agency published a final monograph for OTC stimulant drug products. Any OTC analgesic product containing caffeine for use in restoring alertness or wakefulness will have to follow the dosage and labeling requirements for caffeine established by the agency in that final monograph.

7. One comment from a pharmaceutical firm noted that the firm's name was not included in the list of submissions by firms (42 FR 35348 and 35349). The comment stated that, although this firm did not formally submit data, it presented oral evidence regarding OTC analgesics and underwrote the cost of statistical evaluation of several papers and editorials. To ensure that FDA is aware of the oral evidence that was presented, the comment provided copies of the transcripts of the sessions at which this company presented testimony.

The agency is aware that certain individuals appeared before the Panel to present testimony on behalf of this firm. Their names are included in the list of persons who presented their views to the Panel (42 FR 35347). Because this firm did not submit written data and information in response to the Panel's call-for-data and did not formally submit any data during the course of the Panel's deliberations, it is not included in the list of submissions by firms.

8. One comment, supporting the inclusion of "minor aches and pains of arthritis" in OTC drug analgesic labeling, argued that the Panel decided at an early stage of its review to limit the indications of antirheumatic products to "minor aches and pains" and remove all mention of the minor aches and pains of arthritis. The comment also stated that during the remainder of its review the Panel did not seriously consider any submission or presentation that was not in accord with the Panel's original decision.

The Panel considered the arthritis labeling issue several times during its review, including its April 1976 meeting. The Panel gave reasons for its recommendations on arthritis labeling under its general discussion of the labeling of OTC analgesic, antipyretic, and antirheumatic drug products and also in the discussion of antirheumatic agents (42 FR 35354 and 35453). However, because the agency has decided to allow the phrase "minor pain from arthritis" as an example in the monograph indication for OTC analgesic drug products, the comment's point is moot. (See comment 17 below.)

9. Two comments from the same source requested that the administrative record for the internal analgesic proposed monograph be kept open so that the transcripts or tapes of the closed meetings of the Panel could be reviewed and commented on. The comments stated that these transcripts and tapes were not released by FDA until after the comment period closed.

The original comment's request was dated December 1977. In response to a Freedom of Information (FOI) request (FOI file number F77-15,747), the transcripts and tapes of the Internal Analgesic Panel's closed meetings were made available to the comment source on May 17, 1978, after being reviewed by FDA for deletion of trade secrets, patient names, and other nondisclosable information. Since then the agency has not received from the comment source any new data or information relating to the transcripts or any petition to reopen the administrative record. Transcripts of panel meetings are not included in the administrative record. See 21 CFR 330.10(a)(10). The reasons for this are stated in the preamble to the "Proposal to Designate the Contents and the Time of Closing of the Administrative Record," published in the Federal Register of June 4, 1974 (39 FR 19878), and published as a final rule in the Federal Register of November 8, 1974 (39 FR 39556).

Because of the length of time since the FOI request was granted, the agency sees no reason at this point to consider having the record "kept open." All interested persons may submit written comments for a period of 180 days after the publication of this tentative final monograph. Any comments relating to the transcripts of the panel meetings should state the reasons that would warrant the agency's consideration of the transcripts, notwithstanding the reasons given by the agency for not ordinarily considering them.

B. Comments on Internal Analgesic, Antipyretic, and Antirheumatic Labeling

10. Several comments contended that there is no statutory authority for the codification of exact words to be used in describing the modes of action and the symptoms to be relieved by an OTC drug. The comments stated that existing statutory provisions (15 U.S.C. 1453(a), 21 CFR 201.61, and sections 508 and 502(e) of the Federal Food, Drug, and Cosmetic Act (hereafter referred to as the act) (21 U.S.C. 358 and 352(e)) do not show a congressional intent to authorize FDA to legislate the exact wording of OTC drug claims to the exclusion of other equally accurate and truthful claims for these products, and that section 502(c) of the Act (21 U.S.C. 352(c)) demonstrates a congressional intent to the contrary. The comments argued that any language fulfilling the statutory requirement should be satisfactory, and recommended that FDA provide for more flexibility of wording in OTC drug product labeling by adding the following statement to each list of approved indications: "or similar indication statements which are in keeping with the Panel's Report."

In the Federal Register of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The proposed rule in this document is subject to the labeling provisions in § 330.1(c)(2).

11. One comment argued that the labeling proposed by the Panel contains extensive and complicated wording and may well be contrary to the intention of section 502(c) of the act (21 U.S.C. 352(c)), which states that OTC drug labeling is to be written in terms that consumers can easily understand.

In all of its decisions on labeling, the agency seriously considers the consumer's comprehension of the intended message in the labeling. The agency has thoroughly reviewed the Panel's recommended labeling and has modified it where necessary to make it clearer to consumers. Specific comment is invited on the labeling in this tentative final monograph, including comments on consumer understanding of the wording.

12. Two comments objected to the Panel's recommendation that all inactive ingredients be listed in the labeling of OTC analgesic, antipyretic, and antirheumatic drug products. The comments argued that a list of inactive ingredients in the labeling would be meaningless, confusing, and misleading to most consumers. The comments noted that the act does not require that inactive ingredients of drug products be included on a label and argued that listing these ingredients would crowd out information that is more meaningful to consumers.

The agency agrees that the Federal Food, Drug, and Cosmetic Act does not require the identification of all inactive ingredients in the labeling of OTC drug products. Section 502(e) of the act (21 U.S.C. 352(e)) does require disclosure of active ingredients and of certain ingredients, whether included as active or inactive components in a product. Although the act does not require the disclosure of all inactive ingredients in the labeling of OTC drug products, the agency agrees with the Panel that listing of inactive ingredients in OTC drug product labeling would be useful information for some consumers. Consumers with known allergies or intolerances to certain ingredients would then be able to identify substances that they may wish to avoid.

The Proprietary Association, the trade association that represents approximately 85 OTC drug manufacturers who reportedly market between 90 and 95 percent of the volume of all OTC drug products sold in the United States, has established guidelines (Ref. 1) for its member companies to list voluntarily inactive ingredients in the labeling of OTC drug products. Under another voluntary program begun in 1974, the member companies of The Proprietary Association have been including the quantities of active ingredients on OTC drug labels. The agency is not at this time proposing to require the listing of inactive ingredients in OTC drug product labeling. However, the agency commends these voluntary efforts and urges all other OTC drug manufacturers to similarly label their products.

References

(1) "Guidelines for Disclosure of Inactive Ingredients in OTC Medicines," The Proprietary Association, Washington, July 12, 1984, in OTC Volume 03BTFM.

13. One comment supported, while others objected to, the 10-day limitation on aspirin use recommended by the Panel in § 343.50(c)(1)(i): "Do not take this product for more than 10 days." The supporting comment stated that this recommended warning is consistent with the current medical knowledge of aspirin. Other comments objected to the warning on the grounds that it implies to consumers that aspirin products are unsafe or toxic if taken for more than 10 days; that there is no scientific, medical, or legal justification for the recommendation that chronic arthritis patients see a physician every 10 days; and that a delay of much longer than 10 days is needed before consulting a physician because early examination to rule out serious rheumatoid disease is expensive and does not yield results. The opposing comments also argued that many physicians recommend the use of aspirin beyond 10 days and that the consumer, after reading the 10-day warning, might be reluctant to follow the physician's advice. The following alternative wording was suggested, with the explanation that this warning directs that self-medication should not exceed 10 days: "If pain persists for more than 10 days . . . consult a physician immediately."

The agency points out that the 10-day warning was not intended to apply only to arthritic patients, as one comment appears to have interpreted it. As another comment stated, "* * * self-medication (with analgesic drug products) should not continue for more

than 10 days at one time." The intent of the 10-day warning is to inform all consumers, including arthritic patients, that analgesic drug products should not be taken for more than 10 days "unless directed by a doctor," so that serious conditions do not go undiagnosed and untreated. (See 42 FR 35351.) To reflect this intent, the agency is adding the words "unless directed by a doctor" to the warning for adults in § 343.50(c)(1)(i) and the corresponding warning for children in § 343.50(c)(2)(i). The agency does not believe that these warnings will imply to consumers that analgesic products are unsafe or toxic if taken for more than 10 days (or 5 days for children).

14. One comment supported, and others opposed, that portion of the recommended warning for analgesic and antipyretic products in § 343.50(c)(1)(i) that advises the consumer to consult a physician if symptoms persist or new ones occur. The comment that favored the warning stated that it is consistent with the state of medical knowledge concerning aspirin. One comment opposing the warning argued that informing the consumer to consult a physician if new symptoms occur may unduly alarm the consumer and could burden doctors with additional inquiries from consumers. Another comment stated that new but not unusual symptoms that respond to self-treatment may be expected during the normal course of a self-limited disease, e.g., the fever that develops during a stage of the common cold. The comments suggested the following alternative wording for § 343.50(c)(1)(i) and (ii): "If symptoms persist or get worse, consult your physician"; or "If symptoms persist, or new *unexpected* ones occur, consult your physician."

The agency agrees that worsening symptoms should be mentioned in the warning because this alerts the consumer to consult a doctor when one is needed, e.g., upon the development of secondary infection, rather than only after a 10-day (adults) or 5-day (children) maximum limit for self-treatment. The warning has been amended accordingly. The agency does not believe that informing the consumer to consult a doctor if new symptoms occur would unduly frighten consumers or further burden doctors. For clarity and precision, the agency is revising this portion of the warning to read, "If pain or fever persists or gets worse, if new symptoms occur * * *," in proposed § 343.50(c) (1)(i) and (2)(i). (See comment 18 below for further revision in the warnings.)

15. Two comments agreed with, and many comments objected to, the Panel's recommended Category I labeling indication for internal analgesic active ingredients in § 343.50(a)(1), "For the temporary relief of occasional minor aches, pains, and headache." The comments supporting this limited indication argued that indications that describe specific types of pain mislead the consumer because they imply a treatment of these conditions and encourage inappropriate self-diagnosis and self-treatment. The comments also argued that such labeling suggests to consumers that one product offers unique advantages over another for the specific indications stated on the label.

Some comments objected to the terms "occasional," "minor," or "temporary" because they are unnecessary, indefinite, or meaningless to consumers. Many comments that opposed the recommended indication supported more specific indications that currently appear on many OTC internal analgesic drug products, e.g., "for low back pain," "for muscular aches," "for sinusitis pain," "for pain of sprains," "for functional menstrual pain," "for the relief of minor sore throat pain," and "for pains caused by colds." A consumer survey was submitted to show the need for expanding the recommended indication (Ref. 1).

The comments argued that expanding the labeling would not imply treatment of these conditions, but would aid the consumer in selecting OTC internal analgesic drug products, thereby avoiding the expense of unnecessary visits to a physician and overburdening the health care system. The comments asserted that it is inconsistent for the Internal Analgesic Panel to prohibit the indication "For cold symptoms," while the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products (Cough-Cold Panel) allows this indication for Category I combination products containing internal analgesics. Two comments contended that the use and effectiveness of analgesic ingredients in relieving the pain of sore throat is generally recognized and submitted excerpts of several references to support their statement (Ref. 2).

The Panel recommended a limited indication for OTC internal analgesic-antipyretic drug products in the belief that it was preferable to listing all of the various types of minor pain that these products could be used for. The Panel found that the various claims on the labels it reviewed were often vague and lacked clarity. The Panel was concerned that a plethora of claims would be confusing and misleading to the consumer (42 FR 35355). However, the agency does not believe that a statement describing one or more specific types of pain on an analgesic-antipyretic drug product properly labeled with the active ingredient and with the statement of identity (e.g., "pain reliever-fever reducer") would mislead consumers. Such labeling would be helpful to consumers to provide them with examples of the general types of pain for which OTC internal analgesic drug products are useful. Therefore, the agency is providing manufacturers the option of providing a limited or an expanded indications statement.

For the reasons described below, the agency is proposing the following indications for OTC internal analgesic drug products: "For the temporary relief of minor aches and pains" [which may be followed by one or more of the following: ("associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea)"), or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)")), ("and for the minor pain from arthritis.")] (This statement is further expanded in comment 16 below to include fever labeling.) The types of pain described above are the only ones now being proposed to be allowed in the labeling of OTC internal analgesic drug products. A similar expanded indication is being proposed for products labeled for pediatric use. Minor pain from arthritis is not included as an example in the labeling for pediatric products because when this type of pain occurs in children, it should be treated by a doctor. For the same reason, minor pain associated with backache or muscular aches is not included in the labeling; the underlying cause of these kinds of pain in children should be determined by a doctor. Because the agency does not consider indications concerning premenstrual and menstrual pain appropriate for pediatric analgesic products, these claims are also not being included in the proposed labeling for products for pediatric use.

The terms "muscular aches" and "backache" adequately represent most musculoskeletal aches and pains and are preferable to listing all the specific areas of the body that could be involved. The Panel classified "low back pain" as Category II because it believed that the indication implied to consumers that OTC analgesic drug products could be used to treat arthritic conditions (42

FR 35454 and 35467). However, the agency recognizes that low back pain is not necessarily due to arthritis but may be due to causes amenable to OTC treatment such as minor strains or overexertion. The agency believes that low back pain amenable to treatment with OTC analgesic drug products is appropriately described by the terms "muscle aches" and "backache" in the proposed indication and therefore is not including the claim "low back pain" in the proposed monograph. Because the agency believes that consumers are familiar with the words "low back pain" and proposes to require labeling that would warn consumers against the use of OTC analgesic drug products for more than 10 days and to consult a doctor if symptoms persist or get worse or if new symptoms occur (in § 343.50(c)(1)(i)), the agency would not object to the use of the claim "low back pain" elsewhere on the label provided it is not intermixed with labeling established by the monograph. Similarly, the agency is not proposing to include the claim "pain of sinusitis" in the proposed monograph because it believes that this type of pain is adequately described by the term "headache" in the proposed indication. However, the agency also would not object to the use of this claim provided it is not intermixed with labeling established by the monograph.

Claims relating to sinusitis are addressed in the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products, published in the Federal Register of August 12, 1988 (53 FR 30522). (For a discussion of the agency's decision to include "minor pain from arthritis" in the statement of indications, see comment 17 below.)

Claims relating to menstrual pain were classified in Category II by the Panel (42 FR 35434). However, these claims were also reviewed by the Miscellaneous Internal Panel. The agency has reviewed that Panel's recommendations regarding OTC internal analgesic active ingredients for use during the premenstrual and menstrual periods and concurs with the Panel that any Category I OTC internal analgesic ingredient is safe and effective for the relief of pain associated with the premenstrual and menstrual periods and/or with premenstrual or menstrual cramps. In reviewing the various menstrual claims recommended by the Panel, the agency notes that the Panel placed in Category I a claim "for the relief of pain of dysmenorrhea." However, the agency does not believe that "dysmenorrhea," when used alone, is a word that is commonly understood by consumers. In addition, this word was not used in any of the OTC drug product labeling submitted to the Panel. Therefore, the agency has not provided for its use as a sole indication, but has provided for its optional use parenthetically with other terms, e.g., "* * * minor aches and pains * * * associated with the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea)").

For the reasons discussed in comment 6 of the tentative final monograph for OTC menstrual drug products (published elsewhere in this issue of the Federal Register), the labeling being proposed for these products does not distinguish between the menstrual and premenstrual periods.

The agency is including the claim "sore throat" in the proposed indication after reviewing the various panels' recommendations, and applicable current and proposed regulations. The agency notes that sore throat in most cases is due to a self-limiting condition that resolves itself without treatment. However, the agency is aware that sore throat, mild as it may seem, may be a symptom of a more serious condition that is not amenable to self-diagnosis or self-treatment, such as a streptococcal infection ("strep throat"), which if left untreated may progress to rheumatic fever or acute glomerulonephritis (47 FR 22773). Because of the risk of serious illness if appropriate treatment of a sore throat is unduly delayed, the agency currently recommends that all OTC drug products indicated for the relief of sore throat display the following warning statement: "Warning—severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use for more than 2 days or administer to children under 3 years of age unless directed by physician," (21 CFR 369.20). Although the Internal Analgesic Panel did not specifically address this warning, the agency is proposing to include a modified version in § 343.50 (c)(1)(ii) and (c)(2)(ii) of this tentative final monograph. The agency is proposing to revise the current warning to make it consistent in format with warnings proposed in other current OTC drug tentative final monographs and is proposing that any analgesic drug product labeled for the relief of minor sore throat pain include the following warning. "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly."

Because sore throat accompanied by rash could be indicative of several illnesses not amenable to OTC drug self-treatment, such as rheumatic fever or measles (Ref. 2), the agency believes that consumers should be warned against the use of aspirin when a rash is present. Therefore, the agency is proposing to include the word "rash" in the new proposed warning. The agency is not proposing to include the word "high" as descriptive of fever, as contained in the current warning in 21 CFR 369.20, because the agency believes that it is important for the consumer to recognize the presence of fever associated with sore throat regardless of whether the fever is high or low. The agency is also not proposing to include that portion of the current warning against administering the drug to children 3 years of age without consulting a physician. The Internal Analgesic Panel recommended labeling that provided for the use of analgesics in children 2 years of age. In the tentative final monograph for OTC oral health care drug products, the agency concluded that most Category I anesthetic/anaglesic ingredients, such as benzocaine and dyclonine hydrochloride, could be labeled for the temporary relief of minor sore throat in children 2 years of age or older (53 FR 2458). Therefore, the agency is proposing in this tentative final monograph for the labeling to provide for the use of analgesics for minor sore throat pain in children 2 years of age or older.

The agency is retaining the term "minor" to describe the aches and pains that are amenable to OTC treatment, as opposed to more severe symptoms that should be treated by a doctor. The term "temporary" remains in the indications statement to indicate the type of relief given by OTC internal analgesic drug products.

The term "occasional" is being deleted from the Panel's recommended labeling because the agency believes that the warnings included in the tentative final monograph are sufficient to warn consumers against the chronic use of OTC analgesics unless advised by a doctor.

References

(1) Comment No. C00043, Docket No. 77N-0094, Dockets Management Branch.

(2) Comment No. M00006, Docket No. 77N-0094, Dockets Management Branch.

(3) Berkow, R., editor, "The Merck Manual of Diagnosis and Therapy," 14th Ed., Merck and Co., Rahway, NJ, pp. 81–87, 1976.

16. Several comments objected to the antipyretic active ingredient labeling recommended in § 343.50(a)(2), "For the

reduction of fever," because it does not include the common cold and flu. The comments stated that fever associated with colds and flu is the most common type of fever for which self-medication is appropriate, and that eliminating the terms "common cold" and "flu" from the labeling would deny the consumer necessary information for safe and effective self-medication.

The agency believes that manufacturers should be able to inform consumers of the relationship between the common cold and fever, and is providing a number of options for labeling analgesic-antipyretic drug products so that this can be done if the manufacturer desires. With regard to the term "flu," the agency published a final rule on Reye syndrome and salicylate drug products entitled "Labeling for Oral and Rectal Over-the-Counter Aspirin and Aspirin-Containing Drug Products; Reye Syndrome Warning" in the Federal Register of June 9, 1988 (53 FR 21633). This rule provides that such products labeled solely for use by children (pediatric products) shall not recommend the product for use in treating flu or chicken pox. Because the warning required on all aspirin-containing products includes both children and teenagers (see discussion of final rule earlier in this document) and because of the possibility of teenagers using other than pediatric products, the agency has decided not to add "flu" to the label indications for any aspirin-containing product at this time.

In addition, while FDA noted in the final rule (53 FR 21635) that scientific research to date focuses on the association between Reye syndrome and aspirin, concerns have been raised about the use of the broader category of drug products containing nonaspirin salicylates in children and teenagers with "flu." Therefore, at this time the agency is not proposing to include flu in the labeling indication for any salicylate preparation. However, the labeling prohibition on this "flu" claim does not apply to the internal analgesic-antipyretic ingredient acetaminophen. Therefore, the agency is proposing to include the term "flu" in the indication for acetaminophen.

Section 343.50(a) (2) and (3), as recommended by the Panel, are being deleted, and the Panel's recommended indication for any Category I analgesic/antipyretic ingredient in § 343.50(a)(3) (redesignated § 343.50(b)(1)) is being revised as follows: "For the temporary relief of minor aches and pains" [which may be followed by one or more of the following: ("associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea)"), or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)"))), ("and for the minor pain from arthritis"), and ("and to reduce fever.")] The labeling being proposed for products marketed exclusively for children is as follows: "For the temporary relief of minor aches and pains" [which may be followed by: ("associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," or "toothache")) and/or ("and to reduce fever".)] The agency is also proposing that the term "flu" may be added to these revised indications for products containing acetaminophen.

In addition, the agency is proposing that all OTC analgesic-antipyretic drug products bear a statement of identity as a "pain reliever" or "analgesic (pain reliever)." If the product is also labeled to include the indication "to reduce fever," then the statement of identity is "pain reliever-fever reducer" or "analgesic (pain reliever)-antipyretic (fever reducer)."

17. One comment agreed with the Panel's recommendation that OTC analgesic drugs should not be labeled for the relief of pain from arthritis, adding that such labeling could be misleading to consumers. The comment stated that consumers may equate relief of pain with effective treatment of self-diagnosed "arthritis," thus preventing or delaying the diagnosis and proper treatment of a rheumatic disease and that OTC dosages of aspirin "rarely if ever" have anti-inflammatory activity.

Other comments disagreed with the Panel's recommendation and urged that labeling of OTC antirheumatic products include their use for the temporary relief of minor aches and pains from arthritis and rheumatism for the following reasons: (1) Consumers should not be denied such information, and to do so would place increasing demands on doctors and economic burdens on consumers and the health care system; (2) aspirin has an anti-inflammatory effect at OTC dosages, but the Panel's recommended labeling may lead some consumers to believe that aspirin products are unsuitable for relieving arthritis pain, and they may turn to undesirable treatment alternatives, such as diet fads or copper jewelry; (3) minor arthritic syndromes can be managed by self-medication with OTC internal analgesics without leading to serious medical consequences from delays in treatment of progressive diseases such as rheumatoid or gonococcal arthritis.

The agency agrees that arthritis cannot be self-diagnosed, but recognizes that OTC analgesics are effective in relieving "minor pain" associated with arthritic conditions. Descriptive labeling of this nature is now widely used in the labeling of OTC analgesic drug products, e.g., "for the temporary relief of minor arthritic pain." The agency does not believe that such labeling is misleading to consumers. As discussed in comment 15 above, the agency is proposing to expand the indications for OTC analgesic drug products to include examples of pain amenable to self-treatment, i.e., "headache," "toothache," "muscular aches," "backache," "sore throat," "pain associated with the common cold," "pain associated with the premenstrual or menstrual periods," or "minor pain from arthritis." Although the terms "arthritis" and "rheumatism" are used interchangeably by some consumers, the agency believes that "arthritis" is more accurate, more precise, and more readily understood by the majority of consumers.

Instead of denying consumers information on the use of OTC analgesics for relieving the minor pain from arthritis, the agency believes it would be more appropriate to provide such labeling. Consumers are warned against use for more than 10 days and to consult a doctor if pain persists or gets worse, if new symptoms occur, or if redness or swelling is present. These warnings should be sufficient to encourage consumers with persistent pain or inflammation who believe they have arthritis to consult a doctor for diagnosis and treatment. (See comments 18 and 19 below.)

18. One comment recommended a warning for OTC analgesic drug products that would alert consumers with symptoms of arthritis to consult a doctor if pain persists for more than 5 days or if redness is present.

Because the agency is expanding the indications labeling for analgesic ingredients to include minor pain from arthritis, the warnings recommended by the Panel in § 343.50(c)(1) (i) and (ii) are being revised to alert consumers to symptoms of inflammation (redness or swelling), which may appear in conditions such as arthritis and which signal the need to consult a doctor. Because the indications for pain and fever may be combined, the warnings are also being combined to inform consumers to consult a doctor if pain or fever persists or worsens and to include the 3-day limit for fever. The comment submitted no data to support its request

to shorten the limit of OTC analgesic use for symptoms of arthritis to 5 days. In the absence of such data, the agency proposes to retain the 10-day limit for self-medicating for pain.

Recognizing that certain OTC analgesic drug products may be labeled for use in adults and children, for use in children only, or for use in adults only, the agency is proposing the following warnings in the tentative final monograph to replace those recommended by the Panel in § 343.50(c)(1) and (2):

(1) *For products labeled for adults*—(i) *For products containing any ingredient in § 343.10.* "Do not take this product for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition.

(2) *For products labeled for children 2 years to under 12 years of age*—(i) *For products containing any ingredient in § 343.10.* "Do not give this product for pain for more than 5 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition."

(3) *For products labeled both for adults and for children 2 years to under 12 years of age* * * *. "Do not take this product for pain for more than 10 days (for adults) or 5 days (for children), and do not take for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. Do not give this product to children for the pain of arthritis unless directed by a doctor."

19. Several comments disagreed with the arthritis warning for OTC aspirin drug products recommended by the Panel in § 343.50(c)(3)(i): "Take this product for the treatment of arthritis only under the advice and supervision of a physician." The comments also disagreed with the warning for acetaminophen products recommended in § 343.50(c)(5)(ii): "Do not take this product for the treatment of arthritis except under the advice and supervision of a physician." One comment questioned why the warnings were different and recommended that the warning for aspirin in § 343.50(c)(3)(i) also be used for acetaminophen because both drugs are commonly recommended by physicians for the pain from arthritis.

Other comments opposed identical warnings for aspirin and acetaminophen, but also opposed the warnings recommended by the Panel for both drugs (i.e., § 343.50(c) (3)(i) and (5)(ii)), arguing that these warnings are so similar that consumers probably would not perceive their intended difference. These comments added that the Panel's recommended arthritis warning for acetaminophen may lead consumers to believe that acetaminophen is effective in treating arthritis. Emphasizing that acetaminophen, unlike aspirin, has no anti-inflammatory effect and cannot be used to treat arthritis, one comment suggested that the recommended warning in § 343.50(c)(5)(ii) be replaced with the following: "Do not take this product for the treatment of arthritis." As an alternative to this warning, a comment suggested the following warning: "Do not take this product for the relief of arthritis symptoms except under the advice and supervision of a physician." Another comment suggested that, because aspirin can be used to treat arthritis, the following statement be incorporated with the dosage schedule of OTC aspirin drug products in place of the recommended warning in § 343.50(c)(3)(i): "Dosage for arthritis and rheumatic conditions should be only under the advice and supervision of a physician."

The agency agrees that it may be difficult for consumers to distinguish between the warnings recommended by the Panel for aspirin and acetaminophen. Although aspirin is an anti-inflammatory agent, acetaminophen is not. Consumers might incorrectly interpret the Panel's acetaminophen warning (§ 343.50(c)(5)(ii)) to mean that acetaminophen is effective in the treatment of arthritis. To avoid misinterpretation and confusion, the agency is not including this warning in the monograph. Similarly, the agency does not believe that acetaminophen products should bear the warning recommended by the Panel for aspirin products in § 343.50(c)(3)(i), because consumers could also misinterpret this warning to mean that acetaminophen can be used to treat arthritis. An indication for the relief of "minor pain from arthritis" is being proposed for the labeling of both aspirin and acetaminophen products. However, an indication for the treatment of the arthritis itself is not being proposed for any OTC internal analgesic drug product because such treatment should be conducted only under the supervision of a doctor. Different labeling statements on aspirin and acetaminophen drug products regarding arthritis, as suggested by some of the comments, might encourage self-diagnosis and self-treatment of arthritis. The warning being proposed in § 343.50(c)(1)(i) of this document for all Category I ingredients should lead consumers with arthritis symptoms to consult a doctor for diagnosis and treatment of the condition. (See comments 17 and 18 above.) For these reasons, the agency proposes not to adopt the comments' suggestions and is not including either the Panel's recommended § 343.50(c)(3)(i) or § 343.50(c)(5)(ii) in the tentative final monograph.

20. Two comments maintained that the agency should permit the names of OTC analgesic drug products to reflect the uses of the products. The comments specifically requested permission to include the term "arthritis" in certain product names. One comment disagreed, arguing that product names which specifically refer to "arthritis," such as "arthritis strength," "arthritis pain formula," or "rheumatism preparation," imply that these products are uniquely effective for arthritis and will encourage improper self-diagnosis and inappropriate and potentially hazardous therapy.

The agency agrees that product names can be informative and that they should not be misleading. Medically descriptive product names, e.g., "arthritis pain formula," are not required and are not included in the monograph. These names are considered to be outside the scope of the OTC drug review, but are subject to the provisions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Such terms will be evaluated by the agency in conjunction with normal enforcement activities relating to that section of the act.

21. One comment stated that the labels of OTC analgesic and antipyretic drug products should include a warning that these products suppress the body's defense mechanisms. The comment explained that, although the antipyretic and anti-inflammatory effects of aspirin cause a temporary relief of unpleasant symptoms, the disease process is disguised; valuable defense mechanisms such as inflammation and increased body temperature are impaired; and the illness is thereby prolonged.

The comment submitted no evidence to support the statement that analgesic and antipyretic drug products suppress the body's defense mechanisms and thereby prolong illness, and the agency is aware of none. Therefore, the agency is not proposing to include a warning in the monograph as suggested by the comment. The agency considers the

revised 10-day and 5-day warnings for analgesic drug products in § 343.50(c)(1)(i), (2)(i), and (3) in this tentative final monograph adequate to warn consumers to obtain professional help if symptoms persist or get worse or if new symptoms occur.

22. Two comments objected to the 5-day limitation of use of analgesic and antipyretic drug products by children under 12 years of age in the Panel's recommended warning statement in § 343.50(c)(1)(ii). The comments agreed with the Panel that the period of OTC use of analgesic and antipyretic drugs in children under 12 years of age should be limited, but disagreed over the length of time. Suggested alternatives were 2 or 3 days. One comment argued that this warning implies that OTC analgesic drug products are unsafe or toxic if used longer than 5 days.

The agency is proposing the following revised warning for children 2 years to under 12 years of age in § 343.50(c)(2)(i): "Do not give this product for pain for more than 5 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition," (see comment 18 above).

The comments submitted no data to support their suggestions for shorter time limitations. The Internal Analgesic Panel based its recommendation of a 5-day limitation for children on reports from poison control center data and on computer simulations that demonstrated that the plasma salicylate level could exceed 20 milligrams per 100 milliliters (mg/mL) (a toxic level) "among some smaller children of a particular age category following the recommended dosage schedule after 5 days" (42 FR 35368). The agency believes these data provide sufficient reason to propose the Panel's recommended 5-day use limitation for children.

23. Several comments opposed the number and length of warning statements the Panel recommended for OTC analgesic and antipyretic drug products. One comment expressed concern that an extensive list of warnings for products containing aspirin, compared to a shorter list for acetaminophen drug products, will lead consumers to conclude that aspirin drug products are more toxic and less useful than acetaminophen drug products. Other comments urged FDA to limit warning statements to those that are scientifically documented, clinically significant, and important to the appropriate use of the products by the average consumer. These comments further urged that the statements be combined and condensed for ease of consumer understanding and to avoid label clutter that may cause consumers to ignore cautions and warnings in the labeling. One comment suggested the use of supplementary circulars, etc.

FDA agrees that the warning statements for OTC drug products should be limited to those that are scientifically documented, clinically significant, and important for the safe and effective use of the products by consumers. The agency is requiring warning statements for each ingredient on this basis, not on the basis of a comparable number of warnings for each ingredient. Warning statements are also being combined and condensed whenever possible for ease of consumer understanding. In addition, manufacturers are free to design ways of incorporating all required information in labeling, e.g., using flap labels, redesigning packages, or using a package insert.

24. Many comments opposed warnings that cite organs of the body as possible sites of damage by internal analgesic drug products, with some comments referring specifically to the Panel's recommended liver warning for acetaminophen in § 343.50(c)(5)(i). These comments argued that naming an organ that may be injured from an acute overdose or from excessive use of an analgesic drug would place the responsibility of recognizing organ damage on the consumer, who would then be assuming the role of a physician. The comments further argued that this kind of label warning may be misunderstood and may either alarm or cause anxiety in consumers who use drugs rationally. On the other hand, the comments added, such labeling may provide information that may induce individuals to harm themselves.

The comments favored a single, more general warning for all OTC internal analgesic drug products, such as the following: "Do not take this product for more than 10 days unless directed by a physician. Excessive use over a long period of time may cause permanent injury." One comment suggested that, if such a general warning is not adopted, all OTC drug products should bear labeling which fully discloses the conditions under which damage may occur.

The agency is not proposing to include the general warning suggested by the comments in this tentative final monograph. FDA believes that the self-medicating consumer should be made aware of potential risks of a particular OTC drug product through label warnings. As discussed in comment 25 below, the agency agrees that the warnings need not specify the toxic effects on particular organs of the body that can be caused by acute overdose of a drug, as in a suicide attempt, and is not proposing the Panel's recommended liver warning for acetaminophen in this tentative final monograph. However, the agency concludes that the warnings should include specific information on the known side effects or adverse reactions that may occur from use of the drug according to labeled directions, as well as potential dangers that may occur if the labeled directions are exceeded.

The agency concludes that when medical evidence shows that toxicity is associated with the use of an OTC drug, either within its recommended dosage or when used beyond its recommended time limit or dosage (except for acute overdose), it is appropriate to warn consumers of the potential toxicity. In such cases it may be necessary to include organ-specific warnings as well as general labeling statements.

25. Many comments opposed the liver warning recommended by the Panel for acetaminophen drug products in § 343.50(c)(5)(i), "Do not exceed recommended dosage because severe liver damage may occur." Some comments argued that acetaminophen taken in recommended OTC dosage ranges shows no evidence of hepatotoxicity and that the labeling required in § 330.1(g), "Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately," provides sufficient warning to consumers. The comments expressed concern that the liver warning recommended by the Panel may discourage consumers from ever using acetaminophen and that this warning may also encourage suicidal persons to abuse acetaminophen drug products. The comments also argued that the liver warning is especially inappropriate for children's acetaminophen drug products because there is a lack of documented fatalities and serious liver damage in children from acute acetaminophen overdose. The comments stated there may be differences between the metabolism and pharmacokinetics of acetaminophen in children and adults that would cause children to be less vulnerable to acetaminophen toxicity.

Other comments endorsed the recommended liver warning and pointed out that there are no unique signs of acetaminophen toxicity, such as ringing in the ears (tinnitus), and that symptoms of acetaminophen toxicity do not appear until a few days after the overdose.

Noting that consumers are increasing their use of acetaminophen and that fatalities and liver damage have occurred in children, the comments argued that the recommended warning may discourage consumers from exceeding the recommended daily OTC dosage of acetaminophen and make consumers and doctors aware of the consequence of acetaminophen overdose. One comment, concerned about toxicity from the chronic use of acetaminophen in dosages of less than 4 grams (g) per day, suggested that the proposed liver warning be revised to place additional emphasis on the recommended limit of self-treatment with acetaminophen as follows: "Do not exceed recommended dosage or take for more than 10 days, because severe liver damage may occur." Another comment suggested that the recommended warning be revised to state the dosage that will cause hepatotoxicity, for example, 40 or more 325-mg tablets taken as a single dose.

After evaluating the data and information submitted, the agency has tentatively decided not to adopt the liver warning recommended by the Panel in § 343.50(c)(5)(i). The agency is aware that liver damage can occur from acetaminophen overdosage, as explained by the Panel (42 FR 35414). However, the agency believes that warnings need not include information on the specific toxic effects on organs of the body caused by acute overdose of a drug, as in suicide. (See comment 24 above.) The agency also considers it inadvisable to specify hepatotoxic dosage levels in consumer labeling, as one comment suggested, because such labeling could be suggestive to suicidal individuals.

The agency has noted two reports of hepatotoxicity in children who overdosed on acetaminophen. Arena, Rourk, and Sibrack (Ref. 1) described a 3 year-old girl who ingested 35 tablets of acetaminophen 325 mg and suffered decreased consciousness, vomiting, and enlargement of the liver and spleen. At that time the serum ammonia level was 82 micrograms per deciliter (μg/dL). She was admitted to the hospital about 24 hours after ingestion. The serum acetaminophen level was 94 micrograms per milliliter (μg/mL) 24 hours after ingestion; 48 hours after ingestion it dropped to 26 μg/mL. Seventy-two hours after the overdose, serum transaminase (liver enzyme) levels revealed a peak serum glutamic-oxaloacetic transaminase of 20,376 International Units (I.U.) and a peak serum glutamic-pyruvic transaminase of 13,303 I.U. The patient was alert and in good spirits by the second day in the hospital and was discharged 1 week later. Seven weeks after discharge her liver enzymes were normal.

Although this child weighed only 31 pounds and had ingested 11.375 g acetaminophen, resulting in phenomenal transaminase levels and a high plasma level of acetaminophen at 24 hours, she survived without any aftereffects. As one comment noted, this case suggests that a child's liver may be less vulnerable to the hepatotoxic effects of acetaminophen overdosage than an adult's. The agency points out, however, that before conclusions can be made on the potential toxicity of acetaminophen in children, more data are needed on the metabolism of acetaminophen and clinical observations in children (Ref. 2).

Carloss (Ref. 3) reported the death of a 3½-year-old girl who had an upper respiratory infection and was being treated with acetaminophen. The child was given 120 mg of acetaminophen syrup every 4 hours for three doses. Her doctor later increased the dose to 720 mg every 3 hours. During the next 24 hours she took 5.04 g acetaminophen and was hospitalized for nausea and vomiting. Fourteen hours after the last dose, the acetaminophen level was 5.3 mg/dL (therapeutic range, 1 to 3 mg/dL), well in the range of hepatotoxicity. The child was discharged from the hospital the next morning, but was readmitted 16 hours later with a serum glutamic-oxaloacetic transaminase level of 22,000 I.U. and subsequently died.

The child described by Carloss (Ref. 3) was approximately the same age as the one described by Arena, Rourk, and Sibrack (Ref. 1). Neither child had been treated with an antidote for acetaminophen poisoning, such as *N*-acetylcysteine. It is difficult to explain why the child who had ingested 5.04 g acetaminophen died, and the child who had ingested 11.375 g acetaminophen survived.

Regarding chronic use of acetaminophen within recommended OTC dosages, the agency at this time does not believe that the labeling suggested by the comment, "Do not exceed recommended dosage or take for more than 10 days, because severe liver damage may occur," is needed. The warnings proposed in § 343.50(c) (1)(i) and (3) in this tentative final monograph already state a 10-day limitation for adults on OTC analgesic self-medication. Furthermore, the agency is aware of only one somewhat convincing case report of acetaminophen hepatotoxicity associated with chronic acetaminophen usage in a normal individual (Ref. 4). A second case has been reported, but rechallenge results were inconsistent (Ref. 5). As discussed in detail in comment 27 below, Olsson (Ref. 4) described a 55-year-old male who was hospitalized for a flareup of hepatitis while taking a product containing acetaminophen and chlormezanone. He had no recent history of drug or alcohol use, but had a 1-year history of alcohol abuse 7 years before hospitalization. Because this individual developed hepatotoxicity on a low dose of acetaminophen, it is possible that some other problem was also present. (This patient was using a drug containing acetaminophen and chlormezanone, which could have induced the liver injury.) No similar report has appeared despite the wide use of acetaminophen.

A case of chronic use of 325 mg acetaminophen (12 tablets daily for 1 year) was described in which the patient's serum glutamic-oxaloacetic transaminase level was normal before acetaminophen use (Ref. 5). After 1 year of acetaminophen use, liver function tests showed an abnormal serum glutamic-oxaloacetic transaminase level and enlargement of the liver and spleen. After the drug was discontinued, the patient's serum glutamic-oxaloacetic transaminase level returned to normal. After being discharged from the hospital, the patient resumed using 12 tablets of 325 mg acetaminophen daily. Within 2 months he developed pain and was rehospitalized. A monitored rechallenge with one dose of 1,325 mg acetaminophen caused a rise in liver enzyme levels (serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase levels) within 12 to 18 hours. A liver biopsy revealed "bridging necrosis, spanning two portal and two central areas." After discontinuing acetaminophen for 4 months, the individual developed abdominal pain and enlargement of the spleen and had to be treated with azathioprine and prednisone. One year later, when liver function tests were back to normal, the individual again was rechallenged with 1,325 mg acetaminophen without any development of symptoms or rise in liver enzyme levels. This raises the possibility that this patient might have been developing chronic active hepatitis exacerbated by acetaminophen.

Rosenberg et al. (Ref. 6) described two individuals who had taken 3.6 g acetaminophen daily for 1 to 2 weeks. One person had a history of Gilbert's disease (characterized by mild jaundice). Both developed jaundice during a course of infectious mononucleosis. However, because

jaundice can occur in 5 to 10 percent of patients with infectious mononucleosis, the jaundice in these two patients could not definitely be attributed to acetaminophen.

Johnson and Tolman (Ref. 7) described a patient who had been taking 3 g acetaminophen daily and complained of fatigue and loss of appetite. The patient had used no other drugs and was not exposed to toxins other than unidentified cleaning solvents used occasionally. On medical examination there was liver tenderness, and a liver function test showed abnormal results. A liver biopsy revealed evidence of chronic active hepatitis with cirrhosis. The patient had a positive rechallenge, and the liver enzymes increased during the 2 weeks following the rechallenge, indicating that acetaminophen may have caused this elevation. It is possible that the patient had chronic active hepatitis and that acetaminophen exacerbated it. This case was also complicated by the concomitant occasional use of unidentified cleaning solvents.

The agency has noted instances where only a mild overdose of 5 to 7 g of acetaminophen may have produced hepatotoxicity. Ware et al. (Ref. 8) described a person who developed disorientation, jaundice, and fever after using acetaminophen and prescription drugs daily for headaches. Liver enzyme levels were elevated, and a liver biopsy showed centrilobular fibrosis and bridging necrosis with evidence of both an acute and a chronic process. The patient improved after 8 days of unspecified conservative treatment. This case does not prove acetaminophen hepatotoxicity because the other drugs the patient had been taking can cause hepatitis.

Toxic hepatitis was reported in three persons who were regularly ingesting acetaminophen in higher amounts than the recommended OTC dosage (Ref. 9). One patient was an alcoholic who for years had used up to 10 300-mg tablets of acetaminophen daily. During the 4 days before admission to the hospital, this individual drank no alcohol, but used about 100 tablets of acetaminophen. On admission to the hospital, the patient's liver enzymes were elevated, but they fell rapidly over the next 2 to 3 days. The amount of acetaminophen ingested and the subsequent pattern of serum liver enzyme abnormality found in this patient were consistent with a substantial overdose of acetaminophen 2 to 3 days before admission.

The second individual used as much as 5.2 g acetaminophen daily. This patient had disseminated bronchial cancer, with general ill health and malnutrition. This patient's liver enzymes were elevated while using acetaminophen. After the liver enzymes returned to normal, the patient was rechallenged. The rechallenge of 5.2 to 6.5 g acetaminophen daily produced elevated liver enzyme levels. The plasma acetaminophen level at 24 hours was 37 μg/mL, corresponding to an overdose of the drug.

The third individual had reportedly used 5.2 to 6.5 g acetaminophen daily for 3 weeks before hospitalization. Forty hours after the last dose, the plasma acetaminophen concentration was 15 μg/mL, consistent with an overdose.

Although it is not inconceivable that chronic use of acetaminophen within recommended OTC dosage ranges produces chronic active hepatitis in a very low percentage of people, and although it is possible that acetaminophen can exacerbate preexisting chronic active hepatitis, the agency concludes that the above data do not provide an adequate basis for requiring a labeling statement on liver damage from chronic use of acetaminophen, that is, within recommended daily OTC dosages for longer than 10 days.

Although the liver warning recommended by the Panel in § 343.50(c)(5)(i) is being deleted, the agency shares the comments' concern that symptoms of acetaminophen toxicity do not appear until a few days after an overdose. Following acetaminophen overdosage, there is a 24- to 48-hour period of relative well-being, when symptoms of hepatotoxicity do not appear despite the occurrence of liver damage. This "silent period" may create a false sense of security that could delay the use of an antidote, which must be administered promptly in order to be effective (Refs. 10 and 11). To alert consumers that prompt medical attention is essential to the proper management of acetaminophen overdose, the agency is proposing the following overdose warnings for acetaminophen drug products: For products labeled for adults (§ 343.50(c)(1)(iii)), "Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms," or for products labeled for children (§ 343.50(c)(2)(iii)), "Prompt medical attention is critical even if you do not notice any signs or symptoms." For products labeled both for adults and children, the warning for adults would apply, as described in § 343.50(c)(3). Both warnings would be required to follow the general overdose warnings in § 330.1(g) that are required for all OTC drugs.

References

(1) Arena, J.M., M.H. Rourk, and C.D. Sibrack, "Acetaminophen: Report of an Unusual Poisoning," *Pediatrics*, 61:66–72, 1978.

(2) Peterson, R.G., and B.H. Rumack, "Pharmacokinetics of Acetaminophen in Children," *Pediatrics* (Supplement), 62:877–879, 1978.

(3) Carloss, H.W., "Misuse of a 'Harmless' Drug," *Archives of Internal Medicine*, 139:689–689, 1979.

(4) Olsson, R., "Increased Hepatic Sensitivity to Paracetamol," *Lancet*, 2:152–153, 1978.

(5) Bonkowsky, H.L., G.H. Mudge, and R.J. McMurtry, "Chronic Hepatic Inflammation and Fibrosis Due To Low Doses of Paracetamol," *Lancet*, 1:1016–1018, 1978.

(6) Rosenberg, D.M., et al., "Acetaminophen and Hepatic Dysfunction in Infectious Mononucleosis," *Southern Medical Journal* 70:660–661, 1977.

(7) Johnson, G.K., and K.G. Tolman, "Chronic Liver Disease and Acetaminophen," *Annals of Internal Medicine*, 87:302–304, 1977.

(8) Ware, A.J., et al., "Acetaminophen and the Liver" (letter to the editor), *Annals of Internal Medicine*, 88:267–268, 1978.

(9) Barker, J.D., D.J. de Carle, and S. Anuras, "Chronic Excessive Acetaminophen Use and Liver Damage," *Annals of Internal Medicine*, 87:299–301, 1977.

(10) Rumack, B.H., and R.G. Peterson, "Acetaminophen Overdose: Incidence, Diagnosis, and Management in 416 Patients," *Pediatrics* (Supplement), 62:898–903, 1978.

(11) Ameer, B., and D.J. Greenblatt, "Acetaminophen," *Annals of Internal Medicine*, 87:202–209, 1977.

26. Several comments urged the adoption of a warning statement that advises consumers who have preexisting liver disease, such as hepatitis or infectious mononucleosis, or who may have Reye syndrome, against the use of acetaminophen unless directed by a doctor. The comments cited reports in the medical literature concerning acetaminophen toxicity in persons with liver disease (Refs. 1 through 13). Two comments asserted that there is no evidence to warrant a warning regarding acetaminophen and preexisting liver disease. One of these comments submitted two clinical studies (Refs. 14 and 15) and a report (Ref. 16) to support its position.

In reviewing and evaluating the data and information submitted by the comments, the agency has concluded that there is insufficient evidence at present to propose a warning against the use of acetaminophen at recommended OTC dosages by individuals with preexisting liver disease.

The data and information in Refs. 1 through 7, Refs. 9 through 13, and Ref. 16 presented no evidence to show that OTC dosages of acetaminophen cause

hepatotoxicity in persons with preexisting liver disease. Rosenberg et al. (Ref. 8) described two persons who developed jaundice during a course of infectious mononucleosis. As discussed in comment 25 above, the jaundice cannot be confidently ascribed to acetaminophen.

One of the clinical studies (Ref. 14) presents an open study of six male adults with chronic liver disease who were given 1 g acetaminophen every 4 hours four times a day. After 5 days of acetaminophen administration, there were no significant changes in liver enzyme laboratory values. The mean half-life of acetaminophen in these six subjects was 3.42 ± 2.5. Ten hours after an initial dose of 1 g acetaminophen was administered on the first day, the plasma acetaminophen level was 1.9 ± 1.5 μg/mL. There was no evidence of any significant accumulation of acetaminophen in the plasma of these individuals.

The other clinical study (Ref. 15) presents a placebo-controlled, double-blind, crossover study in which placebo or 4 g acetaminophen (1 g every 4 hours for four doses per day) was administered daily to 20 adults with preexisting liver disease of various types. The individuals were treated for 13 days and crossed over to the alternate regimen without a washout period. In comparing liver enzyme levels of the individuals during acetaminophen administration with those during placebo administration, no statistically significant differences were found. Three patients were excluded from the final analysis. One had changes in liver enzymes which could be attributed to the erratic course of his chronic active hepatitis. Although it is difficult to distinguish enzyme changes because of the erratic course of chronic active hepatitis versus drug-induced changes, the resulting rise in transaminases after rechallenge with acetaminophen raises the question of whether acetaminophen exacerbated this individual's chronic active hepatitis.

Additional data regarding the plasma half-life of acetaminophen in individuals with liver disease were presented at a meeting of FDA's Gastrointestinal Drugs Advisory Committee (Ref. 17). These data appeared to document prolonged serum half-life for acetaminophen in patients with liver disease. Nonetheless, the results of the placebo-controlled crossover study (Ref. 15) gave no evidence that this prolongation results in hepatotoxic levels of the drug. It should be pointed out, however, that prolonged acetaminophen half-life in the patients in this study was not documented, and thus it is not certain that the patients were at risk for possible adverse effects related to such prolongation.

Data pertaining to cytochrome P-450 enzyme levels in patients with liver disease may also be relevant to determining acetaminophen hepatotoxicity. Available data attribute the production of the hepatotoxic metabolite of acetaminophen to the cytochrome P-450 system. A reduction in activity of the cytochrome P-450 system then might result in reduced risk of hepatotoxicity.

The following data show decreased cytochrome P-450 levels in individuals with chronic liver disease. Farrell, Cooksley, and Powell (Ref. 18) showed that the cytochrome P-450 concentrations in patients taking enzyme-inducing drugs such as phenobarbital, phenytoin, and glutethimide are no different in control subjects than in persons with mild-to-moderate hepatitis or inactive cirrhosis. The patients with severe hepatitis or active cirrhosis who were taking enzyme-inducing drugs did have decreased cytochrome P-450 concentrations and may have lost the ability to respond to inducing agents.

Schoene et al. (Ref. 19) measured the cytochrome P-450 content in needle biopsies of the human liver and found that in individuals with severe hepatitis and cirrhosis, the cytochrome P-450 level was 50 percent of the control value. In individuals with either mild or moderate hepatitis, there was no change in the cytochrome P-450 level. Gabrielle et al. (Ref. 20) found no change in the cytochrome P-450 content in individuals with alcoholic steatosis and in those recovering from viral hepatitis compared with normal individuals. The cytochrome P-450 level in chronic persistent hepatitis was 10 percent of the level in the normal individuals. In chronic active hepatitis, the cytochrome P-450 level was 30 percent of that of a normal individual. Although these data suggest that the activity of the cytochrome P-450 system is reduced in individuals with severe liver disease, the relevance of this finding to acetaminophen hepatotoxicity in such individuals is not clear. It is possible that low cytochrome P-450 levels would protect against acetaminophen hepatotoxicity, but the evidence is conflicting on whether acetaminophen exacerbates liver disease.

In summary, the agency believes that at present there are insufficient data to support a warning against the use of acetaminophen by persons with preexisting liver disease such as hepatitis, liver function affected by infectious mononucleosis, or liver disease resulting from Reye syndrome.

References

(1) Ambre, J., and M. Alexander, "Liver Toxicity After Acetaminophen Ingestion," *Journal of the American Medical Association*, 238:500-501, 1977.

(2) Arena, J.M., M.H. Rourk, and C.D. Sibrack, "Acetaminophen: Report of an Unusual Poisoning," *Pediatrics* 61:68-72, 1978.

(3) Ameer, B., and D.J. Greenblatt, "Acetaminophen," *Annals of Internal Medicine*, 87:202-209, 1977.

(4) American Academy of Pediatrics Committee on Drugs, "Commentary on Acetaminophen," *Pediatrics*, 61:108-112, 1978.

(5) Fernandez, E., and A.C. Fernandez-Brito, "Acetaminophen Toxicity," *New England Journal of Medicine*, 296:577, 1977.

(6) Barker, J.D., D.J. de Carle, and S. Anuras, "Chronic Excessive Acetaminophen Use and Liver Damage," *Annals of Internal Medicine*, 87:299-301, 1977.

(7) Johnson, G.K., and K.G. Tolman, "Chronic Liver Disease and Acetaminophen," *Annals of Internal Medicine*, 87:302-304, 1977.

(8) Rosenberg, D.M., et al., "Acetaminophen and Hepatic Dysfunction in Infectious Mononucleosis," *Southern Medical Journal*, 70:660-661, 1977.

(9) Rumack, B.H., "Dr. Rumack Replies" (letter to the editor), *Pediatrics*, 58:918, 1976.

(10) Prescott, L., et al., "Plasma-Paracetamol Half-life and Hepatic Necrosis in Patients with Paracetamol Overdosage," *Lancet*, 1:519-522, 1971.

(11) Prescott, L.F., and N. Wright, "The Effects of Hepatic and Renal Damage on Paracetamol Metabolism and Excretion Following Overdosage: A Pharmacokinetic Study," *British Journal of Pharmacology*, 49:602-613, 1973.

(12) Emby, D.J., and B.N. Fraser, "Hepatotoxicity of Paracetamol Enhanced by Ingestion of Alcohol: Report of Two Cases," *South African Medical Journal*, 51:208-209, 1977.

(13) Riely, C.A., "Drugs and What They Do to the Liver," *Medical Times*, 106:87-92, 1978.

(14) Benson, C.D., "Phase IV Open Pilot Study to Establish the Safety of Acetaminophen in Subjects with Liver Disease," Investigational Protocol, Comment No. C00044, Docket No. 77N-0094, Dockets Management Branch.

(15) Benson, G.D., "The Safety of Acetaminophen in Subjects with Liver Disease," Investigational Protocol in Comment No. C00044, Docket No. 77N-0094, Dockets Management Branch.

(16) Forrest, J.A.H., et al., "Antipyrine, Paracetamol, and Lignocaine Elimination in Chronic Liver Disease," *British Medical Journal*, 1:1384-1387, 1977.

(17) Minutes of the FDA Gastrointestinal Drugs Advisory Committee, Fifteenth Meeting, December 12-13, 1979, included in OTC Volume 03BTFM.

(18) Farrell, G.C., W.G.E. Cooksley, and L.W. Powell, "Drug Metabolism in Liver Disease: Activity of Hepatic Microsomal Metabolizing Enzymes," *Clinical*

Pharmacology and Therapeutics, 26:483–492, 1979.

(19) Schoene, B., et al, "Determination of Drug Metabolizing Enzymes in Needle Biopsies of Human Liver," *European Journal of Clinical Pharmacology*, 4:65–73, 1972.

(20) Gabrielle, L., et al., "Determination of Human Liver Cytochrome P–450: Demonstration of a Micromethod Using Electron Paramagnetic Resonance," *Chemical Abstracts*, 88:249, 1978.

27. Several comments cited data to express concern that certain drugs which induce microsomal enzyme activity (e.g., alcohol and barbiturates) may increase the potential for acetaminophen-induced hepatotoxicity (Refs. 1 through 14). The comments recommended that warnings such as the following be required on the labeling of all products containing acetaminophen:

Do not take this product if you use alcohol or barbiturates unless directed by a physician.

Caution: Do not take this product if you are presently taking a prescription drug for epilepsy, barbiturates, or ethacrynic acid except under the advice and supervision of a physician.

A reply comment opposed the suggested warnings, stating that there is no evidence of any significant drug interaction of acetaminophen when used at recommended doses with drugs which induce microsomal enzyme activity.

The agency is not adopting the suggestion that consumers be warned against the use of ethacrynic acid with acetaminophen. The comments submitted no data to support such a warning, and the agency is not aware of data that indicate a need to warn consumers against the use of ethacrynic acid with acetaminophen.

After reviewing the data cited by the comments, the agency has determined that the results are conflicting and that there is insufficient evidence at this time to warrant a label warning against the use of OTC dosages of acetaminophen products with alcohol, barbiturates, or prescription drugs used for epilepsy.

One comment cited a commentary on acetaminophen which recommended that drugs such as phenobarbital and alcohol should not be used with acetaminophen because they appear to potentiate acetaminophen-induced hepatotoxicity (Ref. 1). However, no firsthand data were presented to support this recommendation. A report by Wilson et al. (Ref. 2) concerned a 13-year-old epileptic who took an overdose of acetaminophen and phenobarbital, subsequently developed hepatic encephalopathy, and died. These authors emphasized the seriousness of dealing with acetaminophen overdose, complicated in this case by the role of phenobarbital in potentiating the hepatotoxicity of acetaminophen.

Wright and Prescott (Ref. 3) retrospectively analyzed data on 16 individuals with hepatic necrosis following acetaminophen overdose. Eight of these individuals showed evidence of ingestion of either alcohol or barbiturates used in the treatment of epilepsy. Three individuals were chronic alcoholics. Wright and Prescott stated that their findings suggest that acetaminophen causes more severe hepatic necrosis in patients who have previously taken drugs that may cause induction of hepatic microsomal enzymes, such as barbiturates and alcohol. However, they conceded that their results must be interpreted cautiously because of the small number of individuals studied and because of uncontrollable factors such as age and nutritional state of the individuals, as well as the possibility of their ingesting other drugs.

Mitchell et al. (Ref. 4) concluded, as a result of their studies in rats and mice, that pretreatment of these animals with phenobarbital potentiates both the incidence and the severity of acetaminophen-induced hepatic necrosis. However, Prescott (Ref. 5) conducted a study on acetaminophen metabolism in 12 healthy volunteers and 15 individuals who were chronically using microsomal enzyme-inducing agents such as phenobarbital and diphenylhydantoin, drugs used in treating epilepsy. Prescott concluded that the production of hepatotoxic metabolites of acetaminophen was not increased in those individuals who used hepatic enzyme-inducing agents. These studies have produced conflicting results which are difficult to reconcile and from which firm conclusions cannot be drawn.

Scott and Stewart (Ref. 6) reported that most of the cases of acetaminophen overdose which they had seen were accompanied by some alcohol use and said that the time available for effective treatment of overdose may be "much reduced" in individuals with alcohol-damaged livers. Barker, de Carle, and Anuras (Ref. 7) observed severe liver damage in an alcoholic who had ingested "moderately excessive" amounts of acetaminophen (100 tablets of 300 mg acetaminophen 4 days before admission to the hospital). These investigators concluded that this individual's use of alcohol induced the formation of toxic acetaminophen metabolites, which made him more susceptible to liver injury from the "moderately excessive" dose of acetaminophen.

Emby and Fraser (Ref. 8) reported on two cases of acetaminophen overdose in alcoholics and concluded that "* * * the enhanced hepatotoxity of paracetamol (acetaminophen) in the presence of enzyme-inducing agents * * * has perhaps not been adequately emphasized." McClain et al. (Ref. 9) conducted studies in mice and also observed the clinical course of three chronic alcoholics who ingested therapeutic, rather than excessive, dosages of acetaminophen. McClain et al. stated that their findings "* * * suggest that alcohol enhances acetaminophen hepatotoxicity in mice and provides supportive evidence that these three alcoholic patients probably had a similar pathophysiological basis for their liver disease." Goldfinger et al. (Ref. 10) reported hepatic damage in an alcoholic who had ingested 9.75 g acetaminophen over a 2-day period prior to hospitalization. Vilstrup et al. (Ref. 11) reported on fulminant liver failure in a woman who was a known abuser of alcohol, diazepam, and barbiturates. The woman had taken a total of 5.4 g acetaminophen over a 2-day period for premenstrual pain and subsequently died.

The agency points out that the amount of acetaminophen ingested by the woman described by Vilstrup et al. is subject to question. It is also difficult to determine the exact daily dosage of acetaminophen ingested by those individuals observed by McClain et al. (Ref. 9) and Goldfinger et al. (Ref. 10). However, it appears that the individuals reported on by McClain et al. and Goldfinger et al. had ingested more than 4 g acetaminophen, which is the recommended maximum daily OTC dosage. In addition, the individual observed by Goldfinger et al. was using meprobamate, another hepatic microsomal enzyme inducer, in addition to alcohol and acetaminophen.

Olsson (Ref. 12) described an individual who had a 1-year history of alcohol abuse (occurring 7 years before hospitalization) and who was hospitalized with jaundice, hepatic cholestasis, and hepatic steatosis. This individual was using a drug containing acetaminophen and chlormezanone. Olsson acknowledged that it was impossible to obtain a reliable drug history from the patient. The role of alcohol is unclear, and chlormezanone could have induced the liver injury seen in this individual. Furthermore, no plasma acetaminophen determination was performed on this individual. Thus it is difficult to implicate acetaminophen and alcohol use positively as the causative factors in this case.

Shamszad et al. (Ref. 13) compiled data that suggest that the half-life of acetaminophen is significantly prolonged in patients with liver disease from alcohol use. However, these investigators noted that when alcohol is used simultaneously with acetaminophen the plasma disappearance curve of acetaminophen is unchanged.

In considering the wide use of acetaminophen in the United States, and after evaluating the above data, the agency concludes that the evidence available to warrant a label warning against the use of OTC dosages of acetaminophen with barbiturates, prescription drugs for epilepsy, or alcohol is conflicting and insufficient. However, if additional data demonstrate the need for such warnings in the future, the agency will reconsider its present position.

References

(1) American Academy of Pediatrics, Committee on Drugs, "Commentary on Acetaminophen," *Pediatrics*, 61:108–112, 1978.

(2) Wilson, J.T., et al., "Death in an Adolescent Following an Overdose of Acetaminophen and Phenobarbital," *American Journal of Diseases of Children*, 132:466–473, 1978.

(3) Wright, N., and L. Prescott, "Potentiation by Previous Drug Therapy of Hepatotoxicity Following Paracetamol Overdosage," *Scottish Medical Journal* 18:56–58, 1973.

(4) Mitchell, J.R., et al., "Acetaminophen-Induced Hepatic Necrosis: Role of Drug Metabolism," *Journal of Pharmacology and Experimental Therapeutics*, 187:185–194, 1973.

(5) Prescott, L.F., "Paracetamol Induction Study," unpublished study, Comment No. SUP012, Docket No. 77N-0094, Dockets Management Branch.

(6) Scott, C.R., and M.J. Stewart, "Cysteamine Treatment in Paracetamol Overdose" (letter to the editor), *Lancet* 1:452–453, 1975.

(7) Barker, J.D., D.J. de Carle, and S. Anuras, "Chronic Excessive Acetaminophen Use and Liver Damage," *Annals of Internal Medicine*, 87:259–301, 1977.

(8) Emby, D., and B. Fraser, "Hepatotoxicity of Paracetamol Enhanced by Ingestion of Alcohol," *South African Medical Journal*, 51:208–209, 1977.

(9) McClain, C.J., et al., "Potentiation of Acetaminophen Hepatotoxicity by Alcohol," *Journal of the American Medical Association*, 244:251–253, 1980.

(10) Goldfinger, R., et al., "Concomitant Alcohol and Drug Abuse Enhancing Acetaminophen Toxicity," *American Journal of Gastroenterology*, 70:385–388, 1978.

(11) Vilstrup, H., et al., "Liver Damage after Paracetamol," *Ugeskrift for Laeger*, 139:831–834, 1977.

(12) Olsson, R., "Increased Hepatic Sensitivity to Paracetamol," *Lancet*, 2:152–153, 1978.

(13) Shamszad, M., et al., "Abnormal Metabolism of Acetaminophen in Patients with Alcoholic Liver Disease" (abstract), *Gastroenterology*, 69:865, 1975.

28. Citing reports in the literature (Refs. 1 through 9) to substantiate their argument, several comments stated that acetaminophen has many adverse effects that should be included in label warnings for products containing this ingredient. These adverse effects include allergic reactions with clinical signs such as skin rashes, drug-induced fever, or asthma attacks associated with cross-sensitivity between aspirin and acetaminophen. Other adverse effects include blood dyscrasias, which are abnormal conditions of the blood. An example is thrombocytopenia, a decrease in the number of platelets. The comments attributed these adverse effects either to allergic reactions or idiosyncratic reactions, which are abnormal reactions peculiar to the individual. They also recommended a label warning to advise consumers who are allergic to acetaminophen not to use products containing that drug, and a label warning to advise consumers who have asthma or are sensitive or allergic to aspirin to consult their physician before using acetaminophen drug products.

Two reply comments disagreed, arguing that clinical experience and the medical literature indicate that adverse effects from acetaminophen are rare and do not support the need for such warning statements. These comments also maintained that some of the references cited are single-case, anecdotal reports and that there is insufficient evidence in most of the cases to establish a cause-and-effect relationship between acetaminophen and the reported reactions.

The agency believes that the warnings which the comments requested are not warranted at this time because there is insufficient evidence that these adverse effects are being caused by acetaminophen. However, if sufficient evidence is presented to warrant new warnings in the future, the agency will act accordingly.

Two of the reports on adverse effects of acetaminophen cited by the comments had also been cited by the Panel and presented no new data for the agency's consideration (Refs. 3 and 4). Some of the reports cited by the comments were single-case reports of thrombocytopenia, which may have resulted from a number of factors, including idiosyncracy, or which may have been caused by agents other than acetaminophen (Refs. 1, 3, and 7). There were three single case reports of skin rash following the use of acetaminophen (Refs. 4, 5, and 9), but no cases of drug-induced fever.

Studies present conflicting data on the occurrence of cross-sensitivity between aspirin and acetaminophen (Refs. 2, 6, 8, 10, and 11). Fisherman and Cohen's study (Ref. 2) contained five cases of cross-sensitivity between aspirin and acetaminophen. These researchers calculated an "intolerance index," which can be used to compare the tendency of various drugs to produce allergic reactions. The index is based on the usual therapeutic dose divided by the minimal dose needed to produce clinical symptoms of intolerance. This result is multiplied by the percent of patients showing intolerance. The calculated "intolerance index" of aspirin was 368 compared with 13.5 for acetaminophen, indicating that there is a low degree of cross-reactivity to acetaminophen in aspirin-sensitive patients.

The Smith study (Ref. 6) also contained five cases of cross-sensitivity between aspirin and acetaminophen. A challenge dose of several common analgesics was given to five aspirin-sensitive patients, two of whom indicated they were sensitive to acetaminophen. Smith measured the change in forced expiratory volume, which is a measure of air flow and pulmonary function, and noted whether rhinitis was present. Three of the patients had statistically significant drops in forced expiratory volume, and four patients also developed rhinitis following acetaminophen administration. This study indicates a potential problem in a person who is highly sensitive to aspirin and who uses analgesic drugs, including acetaminophen, but it does not explain the clinical significance of changes in the forced expiratory volume.

Other studies, not cited by the comments, found no sensitivity to acetaminophen among aspirin-sensitive patients (Refs. 10 and 11). Sampter and Beers (Ref. 10) tested acetaminophen in 182 aspirin-sensitive patients and found no adverse reactions. Other investigators tested 11 aspirin-sensitive patients with therapeutic doses of acetaminophen and found no reaction to acetaminophen (Ref. 11).

Because of the conflicting data on the incidence of cross-sensitivity between aspirin and acetaminophen, the agency is not proposing a warning about cross-sensitivity to other analgesics on the acetaminophen label. Although the potential for allergic reactions to acetaminophen does exist, the agency believes that the following statement in the warnings in § 343.50(c) (1)(i), (2)(i)

and (3) will adequately inform consumers to consult a doctor if an allergic reaction, such as a rash, should occur following the use of acetaminophen: "* * * if new symptoms occur * * * consult a doctor because these could be signs of a serious condition."

References

(1) Eisner, E.V., and N.T. Shahidi, "Immune Thrombocytopenia Due to a Drug Metabolite," *New England Journal of Medicine*, 287:376–80, 1972.

(2) Fisherman, E.W., and G.N. Cohen, "Aspirin and Other Cross-Reacting Small Chemicals in Known Aspirin Intolerant Patients," *Annals of Allergy*, 31:476–84, 1973.

(3) Heading, R.C., "Purpura and Paracetamol" (letter to the editor), *British Medical Journal*, 3:743–44, 1968.

(4) Henriques, C.C., "Acetaminophen Sensitivity and Fixed Dermatitis" (letter to the editor), *Journal of the American Medical Association*, 214:2336, 1970.

(5) Michelson, P.A., "Rash, Weakness, and Acetaminophen," *Annals of Internal Medicine*, 83:374, 1975.

(6) Schmid, W.H., "Acetaminophen-Induced Bronchospasm," *Southern Medical Journal*, 70:590 and 612, 1977.

(7) Skokan, J.D., J.S. Hewlett, and G. C. Hoffman, "Thrombocytopenic Purpura Associated with Ingestion of Acetaminophen (Tylenol)," *Cleveland Clinical Quarterly*, 40:89–91, 1973.

(8) Smith, A.P., "Response of Aspirin-Allergic Patients to Challenge by Some Analgesics in Common Use," *British Medical Journal*, 2:494–496, 1971.

(9) Wilson, H.T.H., "A Fixed Drug Eruption Due to Paracetamol," *British Journal of Dermatology*, 92:213–214, 1975.

(10) Samter, M., and R.F. Beers, "Intolerance to Aspirin: Clinical Studies and Consideration of Its Pathogenesis," *Annals of Internal Medicine*, 63:975–983, 1968.

(11) Szczeklik, A., R.J. Cryslewski, and C. Czneriawska-Mysik, "Relationship of Inhibition of Prostaglandin Biosynthesis by Analgesics to Asthma Attacks in Aspirin-Sensitive Patients," *British Medical Journal*, 1:67–69, 1975.

29. One comment suggested that the professional labeling recommended by the Panel (§ 343.80) be revised to include the indications that the Panel did not place in Category I because of its concern about self-diagnosis. The comment argued that, although self-diagnosis is a valid concern for consumer-oriented labeling, this concern is irrelevant to professional labeling. Another comment suggested that the Panel's recommended warnings listed below be moved from consumer labeling to professional labeling because these statements refer to conditions that [illegible] be diagnosed and supervised by [illegible]he comment concluded [illegible]rnings are irrelevant to a [illegible]h an undiagnosed [illegible]d are not needed once the condition is diagnosed because the consumer is then under the care of a physician who will recommend proper medication and advise against inappropriate medication.

The warnings recommended by the comment for inclusion in professional labeling are as follows:

Section 343.50(c)(3)(i): "Take this product for the treatment of arthritis only under the advice and supervision of a physician."

Section 343.50(c)(3)(iv): "*Caution:* Do not take this product if you have stomach distress, ulcers, or bleeding problems except under the advice and supervision of a physician."

Section 343.50(c)(3)(v): "*Caution:* Do not take this product if you are presently taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis except under the advice and supervision of a physician."

Section 343.50(c)(4)(i): "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician."

Section 343.50(c)(4)(ii): "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician."

Section 343.50(c)(4)(iii): "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician."

The request made by the first comment did not specify the indications it was referring to; therefore, the agency cannot respond.

The agency disagrees with the second comment's suggestion that the warnings listed above be moved to the professional labeling section of the monograph. These warnings are essential for the safe and effective use by consumers of the products to which they apply (with the exception of § 343.50(c)(3)(i), which is being deleted for reasons stated in comment 19 above), and the agency proposes to require them in consumer labeling.

30. One comment stated that the following warnings recommended by the Panel in § 343.50(c) should be eliminated from OTC analgesic and antipyretic drug products that are marketed in children's dosage units as children's products: "Adults: Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician." "Adults: Drink a full glass of water with each dose." "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician."

The comment contended that these statements, clearly intended for adults, are unnecessary and inappropriate for analgesic and antipyretic drug products labeled for children. The comment added that requiring these warnings on small containers (e.g., the 36-tablet size limitation for pediatric aspirin products) will result in smaller print that will make the labeling message less conspicuous, less legible, and less likely to be read and understood by the consumer.

The comment also stated that the words "Children under 12 years" should be eliminated from the recommended warnings in § 343.50 (c)(1)(ii) and (c)(3)(iii)(b), for the reasons given above as well as the reason that the statement is superfluous because pediatric products are defined by the Panel in § 343.3(e) as products for children under 12 years.

The pregnancy warning recommended by the Panel in § 343.50(c)(4)(ii) is obviously not needed in products intended only for use in children. In addition, the pregnancy-nursing warning required for all OTC drugs intended for systemic absorption specifically provides for an exemption for drugs that are labeled exclusively for pediatric use. (See 21 CFR 201.63(c)(2).)

The agency agrees that the warnings for adults limiting use to not more than 10 days and directing them to drink a full glass of water with each dose (§ 343.50(c)(1)(i) and (c)(3)(iii)(a)) are unnecessary in the labeling of products intended only for use in children, as the warnings in § 343.50(c)(1)(ii) and (c)(3)(iii)(b) provide the necessary information for children under 12 years of age. The warnings recommended by the Panel in § 343.50(c)(1)(i) and (c)(1)(ii) are being revised and expanded into three warnings appearing in the tentative final monograph under the following sections: § 343.50(c)(1)(i), for products labeled for adults; § 343.50(c)(2)(i), for products labeled for children 2 years to under 12 years of age; and § 343.50(c)(3), for products labeled both for adults and for children 2 years to under 12 years of age. (See comment 18 above.)

The agency agrees that products that are clearly identified for use in children, e.g., infant drops, children's aspirin or acetaminophen tablets, do not have to be labeled with a statement in the warnings or in the directions specifying that they are for children under 12 years, as had been recommended by the Panel. Because the directions for use for such products do not include dosages for people over 12 years of age or under 2 years of age, further labeling specifying

that these products are intended for use by children from 2 to 12 years of age appears to be unnecessary. Accordingly, new § 343.50(b)(4) is being proposed in the tentative final monograph as follows:

(4) *Other required statements*—(i) *For products labeled only for children 2 to under 12 years of age containing any ingredient identified in § 343.10.* (*A*) The labeling of the product contains, on the principal display panel, either of the following:

(*1*) "Children's (*trade name of product or generic name of ingredient(s)*)."

(*2*) "(*Trade name of product or generic name of ingredient(s)*) for Children."

(*B*) The labeling for adults in § 343.50(d) and the statement "Children 2 to under 12 years of age" in § 343.50(d)(3)(ii) are not required.

31. One comment supported and two comments opposed the part of the warning recommended by the Panel for aspirin drug products in § 343.50(c)(3)(iv) which states, "* * * Do not take this product if you have stomach distress * * * ."

The supporting comment stated that aspirin drug products cause gastrointestinal distress at therapeutic doses and that their labeling should bear a warning to this effect. The opposing comments recommended deleting the term "stomach distress," contending that it has little meaning to consumers. The term is so all-inclusive, the comment maintained, it may discourage consumers from using aspirin for symptoms for which it is indicated. The comments explained that "stomach distress" often accompanies symptoms such as headache or fever, as with the common cold or flu, and that the warning may discourage consumers from using aspirin for these concurrent symptoms. One comment suggested that, as alternative labeling, consumers be warned against the use of aspirin "in cases of stomach ulcer and related symptoms."

Because the agency shares the comments' concern that the general term "stomach distress" can be applied to various symptoms and may have little meaning to consumers, the agency is proposing to delete this term from the warning recommended by the Panel in § 343.50(c)(3)(iv).

Although the agency believes that alternative labeling is warranted, it is not adopting the alternative labeling suggested by one of the comments because the term "related symptoms" is vague and probably has little meaning to consumers. As the Panel pointed out, plain aspirin products can cause stomach discomfort or "stomach problems," such as heartburn, upset stomach, or stomach pain, in certain individuals (42 FR 35387). Plain aspirin can also exert adverse effects on the gastrointestinal tract (i.e., mucosal erosion, ulceration, minor occult bleeding, etc.) which may exacerbate stomach problems associated with underlying gastrointestinal disease. These effects can also be produced by salicylates other than aspirin (42 FR 35417 to 35421).

Regarding buffered aspirin products, the Panel stated that "* * * evidence seems to indicate that buffered aspirin produces a lower incidence of gastric intolerance in some patients but not in all patients who exhibit gastric intolerance with regular (plain) aspirin products" (42 FR 35470). However, the agency notes that the Panel also stated that this evidence is conflicting. In addition, the investigators of another study on the incidence of gastric lesions in rheumatic patients using plain, buffered, or enteric-coated aspirin concluded that buffered aspirin with an acid-neutralizing capacity of 1.9 milliequivalents (mEq) per 325 mg aspirin did not appear to prevent aspirin-induced gastric damage (Ref. 1). However, these investigators stated that more definitive studies are needed which compare various aspirin preparations before any final conclusions are reached.

Another study showed that OTC doses of buffered aspirin tablets containing 6.4 mEq of antacid, which exceeds the amount of buffering present in most currently marketed buffered aspirin products, produced gastric mucosal injury. The investigators of this study concluded that such products offer little protection to the gastric and duodenal mucosa (Ref. 2). Furthermore, the Panel stated that there is evidence that highly buffered aspirin for solution will reduce, but not eliminate, the acute gastric erosions and occult blood loss produced by the local effects of aspirin in animals and humans with no predisposing gastrointestinal disease (42 FR 35471).

For these reasons, the agency tentatively concludes that it is necessary to advise consumers who have persistent or recurring stomach problems (such as heartburn, upset stomach, or stomach pain), which may be symptoms of an underlying gastrointestinal disorder, against using products containing aspirin (plain or buffered) or other salicylates unless directed by a doctor. Accordingly, the Panel's recommended warning in § 343.50(c)(3)(iv) (redesignated § 343.50(c)(1)(v)(B)) is being revised as follows: "Do not take this product if you have stomach problems (such as heartburn, upset stomach, or stomach pain) that persist or recur, or if you have ulcers or bleeding problems, unless directed by a doctor." This warning is also being revised in § 343.50(c)(2)(v)(B) for products labeled for children 2 years to under 12 years of age.

References

(1) Silvoso, G.R., et al., "Incidence of Gastric Lesions in Patients with Rheumatic Disease on Chronic Aspirin Therapy," *Annals of Internal Medicine*, 91:517–520, 1979.

(2) Lanza, F.L., G.L. Royer, Jr., and R.S. Nelson, "Endoscopic Evaluation of the Effects of Aspirin, Buffered Aspirin, and Enteric-Coated Aspirin on Gastric and Duodenal Mucosa," *New England Journal of Medicine*, 303:136–138, 1980.

32. One comment asserted that warning statements for aspirin drug products should be stated separately. The comment stated that the following warning is the most important warning to the consumer and should be displayed alone on the label so that its effect is not diminished: "Warning: Keep this and all medicines out of children's reach. In case of accidental overdose, contact a physician immediately." The comment stated that all other cautions on the use of aspirin drug products should be under a section designated "Cautions."

The agency agrees that the general warnings quoted above are among the most important provided for all OTC drugs to consumers. These warnings are required for OTC drug products in § 330.1(g) (21 CFR 330.1(g)). The agency agrees that manufacturers should consider displaying these warnings separately from other label warnings or highlighting them to attract consumers' attention.

Concerning the use of the terms "warning" and "caution," section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(f)(2)) states, in part, that any drug marketed OTC must bear in labeling "* * * such adequate warnings * * * as are necessary for the protection of users * * *." Section 330.10(a)(4)(v) of the OTC drug regulations provides that labeling of OTC drug products should include "* * * warnings against unsafe use, side effects, and adverse reactions * * *."

The agency notes that historically there has not been consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances either

of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems. Accordingly, the signal word "caution" is being deleted from the Panel's recommended warnings in § 343.50(c)(3) (iv) and (v), redesignated § 343.50(c)(1)(v) (B) and (C) in this proposed monograph.

33. One comment stated that the first sentence of the aspirin hypersensitivity warning recommended in § 343.50(c)(4)(i), "This product contains aspirin," is redundant for products that display the word "aspirin" in the product name or are clearly labeled as containing "aspirin." The comment stated that part of the next sentence in the warning, "Do not take this product if you are allergic to aspirin * * *," is adequate to warn consumers and that the first sentence should be deleted.

The agency agrees with the comment. Because section 502(e)(1) of the act (21 U.S.C. 352(e)(1)) requires that the established name of the active ingredients contained in a product be included in the label, the statement, "This product contains aspirin," would be redundant. Therefore, in the tentative final monograph this statement is being deleted from the warning.

34. Two comments urged that all children's aspirin products be labeled to include a warning that salicylate intoxication can occur from a therapeutic overdose when "aspirin is repetitively administered to infants and young children *at commonly recommended doses and time intervals.*" The comments argued that parents have been inadequately alerted to the hazards associated with the cumulative effects of salicylate in infants and young children and that parents frequently ignore recommended dosage schedules for aspirin because they think this drug can be administered with relative impunity. The comments further argued that parents will often continue to give aspirin to relieve a child's fever when the fever actually may be due to aspirin toxicity. One comment noted that ringing in the ears (tinnitus) has no value as a warning of toxicity in the pediatric age group because it is subjective, and infants and young children cannot alert the parent to its occurrence. For these reasons the following warning was suggested for all aspirin drug products for children: "Do not exceed recommended doses unless directed by your physician. More than six consecutive doses at four-hour intervals can lead to serious complications in a feverish dehydrated infant or young child."

Two reply comments disagreed with these comments. One argued that the Panel's pediatric dosage schedule and its recommended warnings in § 343.50 (c)(1)(ii) and (c)(2) contain instructions that, when heeded by parents, are adequate to prevent overdosage. These comments also stated that overdoses may occur with any drug and that parents must be alerted not to exceed the recommended dosages of aspirin as well as other drugs. The comments agreed that tinnitus has no value as a warning symptom because it cannot be adequately described by infants and children. However, the comments pointed out that there are observable symptoms of aspirin toxicity, such as hyperpnea, which can be described in labeling as "deep and rapid breathing." The reply comments also stated that dehydration should not be included in the labeling because parents cannot diagnose this condition, which is rare and should be diagnosed by a doctor. The comments also maintained that such labeling would confuse the consumer and obscure other necessary information on the label.

The agency does not believe that children's aspirin drug products should be labeled with a warning stating that salicylate intoxication can occur when aspirin is taken in doses within the recommended dosage schedule (therapeutic overdose). The reports of overdose of salicylates cited by the comments showed that poisoning from accidental ingestion occurs more commonly in children over 2 years of age and that therapeutic overdose is more likely to affect children under 2 years of age (Refs. 1, 2, and 3). The label directions recommended by the Panel for aspirin state, "For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician." Thus, parents are alerted to consult a physician before giving aspirin to children under 2 years of age. The physician is responsible for giving parents specific dosage instructions for aspirin given to children under 2 years of age and for warning parents of the potential dangers of exceeding the recommended dose.

For children 2 years of age and older, the Panel developed a new dosage schedule to help prevent therapeutic salicylate overdose. This dosage schedule not only is based upon a maximal dose that provides effective plasma levels for analgesic and antipyretic effects, but also has a safety margin in case of an inadvertent 50-percent increase in dosage. The agency believes that this children's dosage schedule, which has been slightly revised (see comment 58 below), and the revised warnings in § 343.50(c) (2)(i) and (3) provide adequate guidance to parents to prevent overdosage.

As for the additional labeling suggested by the comments, the agency believes that terms such as "dehydrated" and "deep and rapid breathing" have little meaning to consumers and are not appropriate for consumer labeling of aspirin drug products, although they may be used by doctors in diagnosing conditions due to toxicity. The information in the suggested labeling, "Do not exceed recommended doses unless directed by your physician," is provided in the directions for use by the phrase "or as directed by a doctor" or "unless directed by a doctor" after the usual recommended OTC dosage of the product.

References

(1) Craig, J.O., I.C. Ferguson, and J. Syme, "Infants, Toddlers, and Aspirin," *British Medical Journal*, 1:757–761, 1966.

(2) Done, A.K., and A.R. Temple, "Treatment of Salicylate Poisoning," *Modern Treatment*, 8:528–551, 1971.

(3) Tschetter, P.N., "Salicylism," *American Journal of Diseases of Children*, 106:134–146, 1963.

35. One comment contended that the warning not to take aspirin if taking a prescription drug for arthritis should not be included in the Panel's recommended warning in § 343.50(c)(3)(v). The comment further contended that the major responsibility of warning the consumer of drug interactions should rest with the prescribing physician and that the following statement by the Panel (42 FR 35372) should apply: "* * * physicians always carefully control the patient's use of all other medications, thereby negating the need for a warning."

The agency believes that many consumers who take prescription drugs will also use OTC analgesics and antipyretics, such as salicylates, without a physician's advice. These consumers may be unaware of possible interactions between the salicylates and prescription

drugs and need to be alerted to this possibility in the labeling. Based upon the Panel's discussion of the increased potential for gastric ulceration if aspirin is taken along with another anti-inflammatory agent (42 FR 35409), the agency tentatively concludes that the warning on the concurrent use of salicylates with prescription drugs for arthritis is needed and therefore should be retained. The warning is not intended to prohibit such concurrent use, but to alert consumers to consult a doctor first.

36. Two comments objected to the Panel's recommended warning in § 343.50(c)(3)(v) that advises against the use of salicylates concurrently with prescription drugs for the treatment of gout. The comments asserted that the warning should be modified to apply only to the use of salicylates and uricosuric drugs, which are drugs that promote the excretion of uric acid in the urine. The comments argued that allopurinol, commonly prescribed for gout, is a nonuricosuric drug and is compatible with salicylates.

The agency endorses the labeling recommended in § 343.50(c)(3)(v) to alert consumers to consult a physician before using OTC salicylates with several types of prescription drugs, including those used in the treatment of gout. The agency concludes that differentiating between uricosuric and nonuricosuric drugs in the warnings for OTC salicylate drug products would be meaningless and confusing to consumers. Because the agency believes that it is important for consumers to understand the reason for this warning, it is proposing in the tentative final monograph that the information in § 343.50(c)(3)(v) (redesignated § 343.50(c)(1)(v)(C) in this monograph) be identified as a drug interaction precaution and appear as follows: "*Drug Interaction Precaution.* Do not take this product if you are taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis unless directed by a doctor." This precaution has been modified in § 343.50(c)(2)(v)(C) for products labeled for children 2 years to under 12 years of age. For products labeled both for adults and children, the precaution for adults will apply. (See § 343.50(c)(3).)

37. One comment objected to the warning recommended by the Panel for aspirin and salicylate products in § 343.50(c)(3)(v), asserting that the potential for drug interaction is greater than that expressed in this labeling. The comment explained that because the information on drug interactions is increasing, the consumer who is using prescription medication should consult a physician before using any pain reliever. The comment suggested the following alternative labeling, explaining that it is broader and more inclusive than the Panel's labeling and will provide safer coverage to the consumer: "If you are taking any prescription medication, consult your physician before using any pain reliever."

Another comment suggested the general drug interaction warning, "If you are taking any prescription medications, consult your physician before taking this medication."

The agency believes the labeling suggested by the comments is too general, and consumers might completely ignore its message. In addition, the suggested warnings would not alert consumers to the specific types of drugs that may interact with OTC analgesics. As discussed in comment 35 above, the agency will propose specific drug interaction warnings to consumers when necessary for the safe use of an OTC drug product.

38. Some comments opposed and others favored the Panel's recommended warning in § 343.50(c)(4)(i) against the use of aspirin drug products by consumers who have asthma. The opposing comments stated that the references the Panel cited to support the need for the warning were outdated and included no reports of fatal asthma attacks. The comments argued that the warning is unnecessary because only about 2 percent of asthmatics experience an adverse reaction to aspirin. Asthmatics are under a doctor's care, the comments stated, and the doctor should warn them of possible adverse reactions.

A comment from a consumer, who suffers from asthma and had been unaware that aspirin could precipitate asthma attacks, supported the Panel's warning. The comment insisted that it is necessary to warn asthmatics who may also be unaware that an asthma attack may occur with the use of aspirin drug products. Another supporting comment suggested the following alternative warning to avoid creating consumer anxiety: "If you have asthma * * * consult your physician before using any pain reliever."

The agency is proposing the following warning in § 343.50(c)(1)(iv) for products containing aspirin or carbaspirin calcium: "Do not take this product if you are allergic to aspirin or if you have asthma unless directed by a doctor." The Panel stated that aspirin has long been associated with allergic-type reactions, such as asthma in hypersensitive individuals. In certain instances these reactions can be life-threatening and even fatal (42 FR 35397). The consumer's comment reaffirmed the need to warn asthmatic consumers who may not always be alerted to this danger by a doctor.

The agency is not proposing the warning suggested by one comment because it refers to "any pain reliever" and is thus too broad. The medical literature includes a few reports that certain pain relievers other than aspirin may precipitate asthmatic attacks in aspirin-sensitive patients. However, these reports do not agree on the analgesic drugs implicated and the mechanism of action involved (Refs. 1 through 7). The agency concludes that more data and information are needed to determine the need for an asthma warning for pain relievers other than aspirin drug products.

References

(1) "Analgesics and Asthma," *British Medical Journal*, 3:419–420, 1973.

(2) Assem, E.S.K., "Immunological and Non-Immunological Mechanisms of Some of the Desirable and Undesirable Effects of Anti-Inflammatory and Analgesic Drugs," *Agents and Actions*, 6:212–218, 1976.

(3) Fisherman, E.W., and G.N. Cohen, "Aspirin and Other Cross-Reacting Small Chemicals in Known Aspirin Intolerant Patients," *Annals of Allergy*, 31:476–484, 1973.

(4) Smith, A. P., "Response of Aspirin-allergic Patients to Challenge by Some Analgesics in Common Use," *British Medical Journal*, 2:494–496, 1971.

(5) Szczeklik, A., R. J. Gryglewski, and G. Czerniawska-Mysik, "Relationship of Inhibition of Prostaglandin Biosynthesis by Analgesics to Asthma Attacks in Aspirin-Sensitive Patients," *British Medical Journal*, 1:67–69, 1975.

(6) Szczeklik, A., and C. Czerniawska-Mysik, "Prostaglandins and Aspirin-Induced Asthma" (letter to the editor), *Lancet* 1:488, 1976.

(7) Weinberger, M., "Analgesic Sensitivity in Children With Asthma.," *Pediatrics*, 62:910–915, 1978.

39. One comment disagreed with the wording in the Panel's recommended warning for aspirin and other salicylate products in § 343.50(c)(3)(ii), "Stop taking this product if ringing in the ears or other symptoms occur." The comment argued that the consumer should not be advised to stop taking the product if tinnitus develops because many doctors use tinnitus as a guideline for adjusting a patient's dosage level of aspirin to a therapeutically effective and tinnitus-free level. The comment stated that the phrase "or other symptoms occur" should be deleted from the warning because it is vague and confusing to the consumer. The comment suggested the following alternative: "If ringing in the

ears develops, consult your physician before taking any more medication."

The agency agrees that it is more appropriate to direct consumers with tinnitus to consult a doctor before taking more medication than to "stop taking" the product. The warning is being revised accordingly in the tentative final monograph. In addition, the phrase "or other symptoms occur" is being deleted from the warning because this phrase is synonymous with the phrase "if new symptoms occur," which has been included in the warnings in § 343.50(c)(1)(i), (2)(i), and (3).

The Panel noted that because aspirin or other salicylates produce a reversible ototoxicity manifested by deafness, it is important that patients who are regularly receiving salicylates at higher dosages be monitored by a physician for hearing loss as well as tinnitus. It is particularly important that patients with preexisting hearing loss be frequently monitored because they will not report tinnitus as plasma salicylate levels increase to toxic levels. An example of this was shown in a report from a consumer with a preexisting hearing loss who described a severe additional loss of hearing after using 50 grains (3,250 mg) of enteric-coated aspirin daily for a month (Ref. 1).

In view of the above considerations, the agency proposes to revise the warning, "Stop taking this product if ringing in the ears or other symptoms occur," to read as follows in § 343.50(c)(1)(v)(A) and (2)(v)(A): "If ringing in the ears or a loss of hearing occurs, consult a doctor before taking (giving) any more of this product."

Reference

(1) Letter from a consumer, included in OTC Volume 03BTFM.

40. One comment suggested that the term "bleeding problems" in the Panel's recommended warning in § 343.50(c)(3)(iv) be changed to "blood clotting problem." The comment argued that the term "blood clotting problem" is more accurate medically and would be more useful to consumers than "bleeding problems," which could be interpreted to include a minor cut that bleeds somewhat longer than usual. The comment provided three references to support its position (Refs. 1, 2, and 3).

The references provided by the comment do not suggest that the term "blood clotting problem" has more meaning to consumers than the term "bleeding problems." Two discuss bleeding time and other laboratory measurements (Refs. 1 and 2); the third discusses the side effect of gastrointestinal bleeding from aspirin use (Ref. 3).

The agency believes that the term "bleeding problems" as used in the warning in § 343.50(c)(3)(iv) (redesignated § 343.50(c)(1)(v)(B)) is accurate and useful to consumers. The Panel recommended the wording in this section to warn persons who have bleeding problems that they should not take aspirin except under the advice and supervision of a physician. Persons with bleeding problems such as hemophilia, von Willebrand's disease, thrombosthenia, or thrombocytopathia may react to aspirin drug products with a markedly prolonged bleeding time that might lead to a significant loss of blood in the gastrointestinal tract or elsewhere.

References

(1) Ingelfinger, F. J., "The Side Effects of Aspirin," *New England Journal of Medicine*, 290:1196–1197, 1974.

(2) Kaneshiro, M. M., et al., "Bleeding Time After Aspirin in Disorders of Intrinsic Clotting," *New England Journal of Medicine*, 281:1039–1042, 1969.

(3) Sanfelippo, M. J., and C. V. Hussey, "Thrombopathy: Identification and Distribution," *American Journal of Clinical Pathology*, 61:628–638, 1974.

41. One comment urged that the labeling of aspirin tablets direct consumers to take these products with food or milk. The comment personally attributed an incident of gastrointestinal bleeding to taking aspirin tablets with water rather than with milk or food, and maintained that food or milk would have coated the stomach and prevented the bleeding.

The comment submitted no data to support its viewpoint. The Panel considered whether salicylates should be taken with food, but concluded that it was most important that solid, oral dosage forms containing salicylates be taken with water to lessen the chance of gastric irritation (42 FR 35356). In fact, the Panel recommended the following warnings in § 343.50(c)(3)(iii): (*a*) "Adults: Drink a full glass of water with each dose," and (*b*) "Children under 12 years: Drink water with each dose."

The Panel specified a full glass of water for adults for each dose of salicylates. At gastric pH, 8 ounces or more of water is required to dissolve a dose of aspirin, the most commonly used salicylate. Undissolved salicylate in contact with the gastric mucosa is one cause of gastric irritation following salicylate ingestion. Although salicylate solution is less irritating than undissolved salicylate, the solution could also be irritating to the highly sensitive individual (42 FR 35387). Solid foods would delay the dissolution of salicylates, allowing the undissolved salicylate to remain in contact with the gastric mucosa longer, but liquid foods, such as juice or milk, dissolve salicylate. However, the agency is concerned that, because of their acidity, taking some juices with aspirin may cause more irritation to the stomach than taking aspirin with water. Also, the agency is unaware of any data showing that milk will lessen the gastric irritation caused by aspirin. Therefore, the agency concurs with the Panel that consumers should be advised to take solid, oral dosage forms of salicylates with water to lessen the chance of gastric irritation. The agency believes that these statements belong under the directions for use, rather than in the warnings. Consequently the warnings recommended by the Panel in § 343.50(c)(3)(iii) (*a*) and (*b*) have been designated as directions in § 343.50(d)(3)(i) and (ii) of this tentative final monograph.

42. Two comments urged Category II status for the following labeling claims for buffered aspirin: "Buffering agents to help make the pain reliever more gentle to the stomach," "helps prevent the stomach upset often caused by plain aspirin," "* * * provides ingredients that may prevent the stomach distress that plain aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label," "faster to the bloodstream than plain aspirin," and claims implying more rapid analgesia as a result of an increased absorption rate.

The comments pointed out that the Panel concluded that there is insufficient evidence to substantiate the claims that buffered aspirin or highly buffered aspirin for solution (aspirin and antacid) can be safely used by persons who should not use plain aspirin. The comments stated that these claims may lead consumers to think that buffered aspirin products either give faster or greater pain relief than plain aspirin or cause less or no stomach distress. The comments expressed concern that reliance on claims relating to less stomach distress with buffered aspirin products could lead to a clinical danger in alcoholics and in persons who are prone to ulcers. Referring to claims such as "gets to the bloodstream faster than plain aspirin," the comments argued that blood level studies do not constitute acceptable scientific evidence to show that buffered products of this type are therapeutically superior to plain aspirin.

Other comments urged Category I status for the above labeling claims for buffered aspirin, stating that consumers should be informed of the purpose of buffering, and requested that the agency

provide specific information on the criteria for achieving Category I status for these Category III labeling claims. The comments noted that the Panel stated that the evidence, although conflicting, seems to show a lower incidence of stomach upset produced by buffered aspirin in some patients who exhibit gastric intolerance to plain aspirin (42 FR 35470). The comments also noted that such labeling claims are qualified or modified by the words "may" and "occasionally" and the phrase "* * * but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on this label." The comments contended that the Panel classified stomach upset claims for buffered aspirin as Category III because the Panel believed that the benefits from the use of buffered aspirin in such instances affect only a few consumers, and not because such claims imply that buffered aspirin products have a therapeutic advantage over plain aspirin.

The comments also contended that there is no proof of a lack of relationship between variations in bioavailability of aspirin products and their resultant clinical effect. The comments argued that if a buffered aspirin product is absorbed more rapidly than plain aspirin and provides the consumer with some therapeutic advantage, labeling claims regarding faster absorption, such as "faster to the bloodstream than plain aspirin," would not be misleading to consumers and should be allowed.

The agency's response to these comments covers all buffered aspirin products, including aspirin with antacid products (such as highly buffered aspirin for solution), because the labeling claims apply to all such products.

The Panel found (1) "Comparisons of the most commonly used plain and buffered aspirin show that salicylate blood levels are twice as high in the first 10 to 20 minutes for the buffered aspirin product compared to regular aspirin," (2) "The basic problem is that there are no well-controlled clinical studies that unequivocally prove or disprove that these differences in absorption will result in clinically important differences in the onset, intensity or incidence of relief of pain or fever," and (3) Category III should be used to classify claims which cannot be fully evaluated with present data but have some reasonable basis and can probably be evaluated by further testing, perhaps involving more sensitive methodology." (See 42 FR 35480.) The Panel also expressed concerns that such claims could be confusing to the public.

The agency concurs that the studies submitted to the Panel are inconclusive to support a claim of more rapid action. The agency concludes that although there were apparent higher blood salicylate levels for buffered aspirin in some studies, there remains insufficient evidence on the basis of controlled clinical analgesic studies, that buffered aspirin products provide a more rapid onset, greater peak intensity, or a more prolonged duration of analgesia than unbuffered aspirin. Because no new data have been submitted to answer the Panel's concerns, claims such as "faster to the bloodstream than plain aspirin" remain classified in Category III.

Further, based upon the data submitted to the Panel, the agency concludes that there is not sufficient evidence to clearly demonstrate that buffered aspirin may help those individuals subject to stomach upset associated with aspirin ingestion. The Panel noted that the results, of the clinical studies comparing buffered aspirin to plain aspirin in which the symptom of gastric intolerance was evaluated, appear to be conflicting, but that the data seemed to indicate that buffered aspirin produces a lower incidence of gastric intolerance in some sensitive individuals. (See 42 FR 35480.) Accordingly, the Panel classified the following label claim in Category III: "Provides ingredients that may prevent the stomach distress that plain aspirin causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label."

Citing the significant variation in dissolution rates among marketed formulations of buffered and unbuffered aspirin products, the Panel stated that the clinical evidence for a given buffered aspirin product could not necessarily be extrapolated to other buffered aspirin formulations. In addition, the Panel noted studies that suggest that an adequately buffered aspirin product may not have an advantage over a well formulated unbuffered product (42 FR 35375). The Panel recommended that specific standards be established for both buffered and unbuffered aspirin products (42 FR 35469). The Panel was uncertain about whether the observed decrease in gastric intolerance of buffered aspirin products was due to the buffering effect on the pH of the microenvironment surrounding the dissolving particles on the stomach lining, the increased dissolution rate, or both. Based on these uncertainties, the Panel stated its opinion that the Category III label claim could be used provided the minimum requirements for buffering capacity (1.9 mEq of acid neutralizing capacity per 325 mg aspirin) are met and the product had a dissolution rate similar to the buffered aspirin used in most of the clinical studies reviewed by the Panel (42 FR 35469 and 35470).

At this time, based upon the data that have been reviewed, the agency agrees that the clinical evidence is inconclusive to support a claim of better gastrointestinal tolerance for buffered aspirin products. However, industry has provided additional data in the form of three new clinical studies (Ref. 2). Detailed information on the disolution profiles and acid neutralizing capacity of the formulations used in these studies were also provided. These data are currently undergoing review by the agency, and will be discussed in the preamble to the final rule for OTC internal analgesic, antipyretic, and antirheumatic drug products.

It should be further noted that after the Panel's report was published, standards for acid neutralization (which is the Panel's recommended standard for acid neutralization for buffered aspirin products) and dissolution rates of buffered aspirin tablets were added to the United States Pharmacopeia (U.S.P.) (Ref. 1). As discussed in comment 98 below, the agency is proposing to incorporate these standards in the internal analgesic monograph. Products that meet these U.S.P standards are identified as "Buffered Aspirin." Accordingly, for buffered aspirin products meeting these standards, the agency is providing for the optional statement "contains buffering ingredients" in this tentative final monograph.

The agency agrees with the comment that consumers should be informed of the purpose of buffering. However, the clinical studies reviewed by the Panel and the Agency, are inconclusive. Until the new data (Ref. 2) are fully evaluated, claims regarding decreased gastric irritation are classified in Category III.

References

(1) "United States Pharmacopeia XXI—National Formulary XVI," Supplement 4, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 2131, 1986.

(2) Comment No. SUP00032, Docket No. 77N-0094, Dockets Management Branch.

43. One comment requested that the claim "faster to the bloodstream than plain aspirin" be allowed for powder dosage forms of aspirin. The comment noted that the Panel acknowledged the rapid absorption of powders by stating: "They [powders] are rapidly absorbed however, often reaching peak blood levels more rapidly than the tablet dosage form" (42 FR 35376). The comment stated that clinical studies

comparing the absorption of an aspirin powder with absorption of aspirin tablets were submitted to the Panel, but there is no indication in the monograph that the Panel considered these studies. The comment also provided a more recent clinical study to support its contention that aspirin in powder form is more quickly absorbed than plain aspirin tablets (Ref. 1).

The studies to which the comment referred were reviewed by the Panel (Ref. 2). Based on these studies and other information, the Panel stated that powders, because of their large surface area, are rapidly absorbed and may often reach peak blood levels more rapidly than tablets.

The additional study submitted by the comment compares the rate of absorption of five different oral aspirin formulations—three in tablet form and two in powder form (Ref. 1). Three minutes after dosing, blood concentrations were higher with the powdered formulations than the tablet formulations. Over a 15-minute period, the powdered aspirin formulations and one buffered aspirin tablet formulation provided the highest blood levels of aspirin.

After considering the above data and information, the agency concurs with the Panel's statement that powders may often reach peak blood levels more rapidly than a tablet dosage form. However, the Panel also concluded that there was a lack of clinical studies that would prove or disprove that such differences in absorption will result in clinically important differences in the onset, intensity, or incidence of relief of pain or fever (42 FR 35480). As discussed in comment 42 above, the agency agrees with the Panel. Because the comment provided no clinical data that demonstrate a relationship between faster absorption and faster or enhanced pain relief, the claim "faster to the bloodstream than plain aspirin" is classified in Category III for powder dosage forms of aspirin. The agency has determined that for this claim to have clinical significance to consumers and to be included in the monograph, data are needed that establish that this effect makes a difference in the onset, intensity, or incidence of relief of pain or fever.

References

(1) Babish, J.G., "A Blood Absorption Study on Aspirin Formulation," draft of unpublished report in Comment No. C00032, Docket No. 77N-0094, Dockets Management Branch.

(2) OTC Volume 030058.

44. One comment requested that the following Category III labeling claims for buffered aspirin products be allowed for carbaspirin calcium: "Faster to the bloodstream than plain aspirin" and "provides ingredients that may prevent the stomach distress that plain aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label." To support its request, the comment pointed out that the Panel concluded that carbaspirin calcium (formerly calcium carbaspirin) has a more rapid dissolution rate than aspirin and that slightly less gastrointestinal bleeding may result from its use (42 FR 35417).

Although carbaspirin calcium may produce slightly less gastrointestinal bleeding than aspirin, the agency notes that the Panel found no evidence that gastric bleeding is related to gastric upset (see comment 46 below); therefore, decreased gastrointestinal bleeding is not sufficient evidence to prove that carbaspirin calcium may be indicated when aspirin cannot be tolerated. With regard to rate of dissolution, the Panel reported on a study by Levy and Hayes that showed that the dissolution half-time of calcium acetylsalicylate carbamide complex (carbaspirin calcium) is the same as that of aspirin buffered with aluminum glycinate and magnesium carbamide (Ref. 1). The authors stated that the incidence of local gastric irritation and the absorption rate of a drug is a function of its dissolution rate (in its particular dosage form). While the results of the study by Levy and Hayes (Ref. 1) are indicative of the rapid dissolution of the product used in the study, an in vitro dissolution test alone is not adequate to support the use of the stomach distress claim for this ingredient. Moreover, because dissolution rates can be significantly influenced by product formulation, the results cannot be extrapolated to other formulations containing carbaspirin calcium. In the absence of any supporting clinical data, the agency is not proposing to include the claim, "provides ingredients that may prevent the stomach distress that plain aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label" for this ingredient in the tentative final monograph and classifies the claim in Category III.

As discussed in comment 42 above, the agency agrees with the Panel that there is a lack of clinical studies to demonstrate that differences in absorption will result in clinically important differences in the onset, intensity, or incidence of the relief of pain or fever. Similarly, the agency concludes that the data are not sufficient to demonstrate that differences in dissolution will result in a clinically important difference in analgesia. Therefore, the agency classifies the claim "faster to the bloodstream than plain aspirin" in Category III for this ingredient. The agency has determined that for this claim to have clinical significance to consumers and to be included in the monograph, data are needed that establish that this effect makes a difference in the onset, intensity, or incidence of relief of pain or fever.

Reference

(1) Levy, G., and B.A. Hayes, "Physicochemical Basis of the Buffered Acetylsalicylic Acid Controversy," *New England Journal of Medicine*, 262:1053–1058, 1960.

45. One comment requested that the following claims for choline salicylate be permitted as Category I labeling: "Acts five times faster than aspirin," "reaches peak action twelve times faster than aspirin," "does not cause the gastrointestinal bleeding associated with the administration of aspirin and other salicylate compounds," "causes less gastric irritation," and "may be taken on an empty stomach and may prevent the stomach distress that aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label." The comment pointed out that the Panel referred to studies showing that choline salicylate does not cause as much gastric bleeding as aspirin and that there is a lower incidence of gastrointestinal distress after choline salicylate administration than after aspirin administration (42 FR 35419). The comment noted that the claims "acts five times faster than aspirin" and "reaches peak action twelve times faster than aspirin" are included in the approved new application (NDA) labeling of choline salicylate.

The OTC drug product referred to by the comment as being the subject of an NDA was approved in 1959. The product was further evaluated under the Drug Efficacy Study Implementation (DESI) Program by the Panel on Neurological Drugs and the Panel on Drugs Used in Rheumatic Diseases. The agency published the Panels' findings in the Federal Register, of April 20, 1972 (37 FR 7820). The Panel on Neurological Drugs concluded that adequate studies showed that blood salicylate levels after choline salicylate administration were 5 times as high in 12 minutes and twice as high in 30 minutes but that there were no clinical studies to show that the onset of analgesic action was sooner, greater, or

more prolonged than with aspirin (37 FR 7823). In the same Federal Register, the agency stated that any further action on the product was deferred pending completion of the OTC drug review (37 FR 7820).

The Internal Analgesic Panel reported on several studies that indicated that choline salicylate is more rapidly absorbed than aspirin. However, the Panel reached the same conclusion as the DESI Panel on Neurological Drugs that there is a lack of clinical studies to demonstrate that more rapid absorption will result in a significant clinical effect (42 FR 35418). As discussed in comment 42 above, the agency concludes that the claim "faster to the bloodstream than plain aspirin" is a Category III claim because of the lack of such clinical data. Similarly, the agency concludes that the data are not adequate to support the claims "acts five times faster than aspirin" and "reaches peak action twelve times faster than aspirin." The agency notes that the Panel concluded that such claims should be classified in Category II. However, the Panel also concluded that Category III should be used to classify claims that have a reasonable basis and probably can be evaluated by further testing (42 FR 35435 and 35480). The agency concludes that such a reasonable basis exists and that such claims should be classified in Category III. The agency has determined that for this claim to have clinical significance to consumers and to be included in the monograph, data are needed that establish that this effect makes a difference in the onset, intensity, or incidence of relief of pain or fever.

Regarding the claims concerning the effect of choline salicylate on the stomach, the Internal Analgesic Panel concluded that based on its review of the submitted data further testing was required to substantiate claims such as "may be taken on an empty stomach and may prevent the stomach distress that aspirin occasionally causes" and proposed a Category III classification for such statements (42 FR 35418). The Panel did note that choline salicylate like highly buffered aspirin is ingested as a solution and may have a performance action similar to highly buffered aspirin for that reason. In the absence of any new supporting clinical data, the agency is placing the above labeling statement and the related claim "causes less gastric irritation" in Category III.

The agency is not proposing to include in the monograph the claim "does not cause the gastrointestinal bleeding associated with the administration of aspirin and other salicylate compounds." This statement refers to occult bleeding. The agency believes that allowing this claim may confuse or unduly alarm consumers by implying that aspirin frequently or commonly causes overt bleeding (or hemorrhaging) from the gastrointestinal tract. The agency believes that this claim is not appropriate for use in the labeling of OTC internal analgesic drug products containing choline salicylate and therefore proposes that this claim be classified as Category II.

46. One comment requested that products containing magnesium salicylate be allowed to claim that this ingredient has less potential to cause irritation of the gastrointestinal tract than aspirin. The comment contended that a submission to the Panel contained enough data to justify this claim (Ref. 1) and provided a letter from a physician stating that his clinical experience shows that patients tolerate magnesium salicylate better than aspirin. The comment also cited magnesium salicylate's physicochemical characteristics as additional support for the claim that it produces less gastrointestinal irritation than aspirin, explaining that magnesium salicylate goes into solution at a higher pH than aspirin and the magnesium ions may provide some buffering capacity.

The data reviewed by the Panel and cited by the comment included a human study in which a gastrocamera showed that both magnesium salicylate and aspirin caused some irritation of the mucous membranes of the stomach. However, the Panel concluded that the results of the study showed no significant difference in the degree of irritation between the ingredients. From other human studies, using radioactive chromate labeling of red blood cells, the Panel concluded that magnesium salicylate might produce less gastrointestinal bleeding than aspirin (42 FR 35419). However, the Panel concluded that there is no evidence that gastric bleeding is related to gastric upset and that these studies are not sufficient to prove that magnesium salicylate may be indicated when aspirin cannot be tolerated. The agency agrees with the Panel's conclusions. Because no new information has been submitted, the agency is placing the claim that magnesium salicylate has less potential for causing gastrointestinal irritation than does aspirin in Category III. Adequate clinical studies are necessary to support such a claim.

Reference

(1) OTC Volume 030042.

47. Several comments supported the Panel's recommendation against concurrent analgesic-antacid labeling claims for highly buffered aspirin for solution and urged adoption of the stomach distress warning recommended in § 343.50(c)(3)(iv). The comments stated that highly buffered aspirin for solution can cause gastrointestinal distress (stomach distress), peptic ulceration, and massive gastrointestinal bleeding and that the risk of gastrointestinal bleeding increases when this product is used with alcohol. The comments cited a "personal communication" and published studies (Refs. 1 through 5) to support this concern.

Other comments opposed the Panel's recommendation and argued that highly buffered aspirin for solution can be safely used to relieve concurrent symptoms of headache and upset stomach. The comments stated that this drug product does not cause mucosal erosions, and does not cause massive gastrointestinal bleeding, with or without alcohol. The comments stated that the "stomach distress" warning would preclude the marketing of these products for concurrent symptoms of headache and upset stomach. One comment expressed concern that if a highly buffered aspirin for solution cannot be marketed for concurrent symptoms of headache and upset stomach, consumers will substitute less widely used and tested products containing acetaminophen and antacid.

Highly buffered aspirin for solution contains a sufficient quantity of buffering ingredients to conform to the specifications for antacids established in the final monograph for OTC antacid drug products (21 CFR 331.10). Such products have been marketed for consumers with symptoms that require both an analgesic and an antacid, such as headache with heartburn or headache with "upset stomach."

In the final monograph for OTC antacid drug products published in the Federal Register of June 4, 1974 (39 FR 19869), the agency concluded that there is a significant target population for which a combination product containing a salicylate and an antacid provides rational concurrent therapy. The agency further concluded that because the safety evidence for the use of analgesic-antacid combination products is derived from studies and experience with products intended for administration as a solution, the use of these combinations for concurrent symptoms should be limited to these types of products (39 FR 19869 and 19875). When the final monograph for OTC antacid drug

products was published, the agency had received no data to show that such a combination product would be unsafe to use for concurrent symptoms, nor have such data been received since publication of the advance notice of proposed rulemaking for OTC internal analgesic drug products. The agency has also not received any data showing that highly buffered aspirin for solution presents the risk of massive gastrointestinal hemorrhage or that using these products with alcohol increases the risk of massive gastrointestinal bleeding in normal individuals. References 1 through 5, cited by one comment, discuss the association of alcohol and aspirin products with gastrointestinal bleeding, but do not provide sufficient evidence that the use of highly buffered aspirin and alcohol is associated with massive gastrointestinal bleeding. The agency could not assess the "personal communication" because the comment did not provide a copy.

The agency concurs with the Internal Analgesic Panel's recommendation that aspirin products should not be used by consumers who have ulcers, bleeding problems, or recurring or persistent stomach problems. This recommendation is supported by the findings of a study on gastrointestinal hemorrhage in persons with stomach problems who used an aspirin-antacid for solution combination product (Ref. 6). However, the agency finds a lack of data to preclude the use of aspirin-antacid products as an analgesic-antacid for concurrent symptoms of headache and heartburn, etc., provided the product is intended for ingestion as a solution and provides at least 5 mEq of acid-neutralizing capacity (as specified in § 331.10(a)). Therefore, the agency is proposing that any highly buffered aspirin for solution or other aspirin-antacid product for solution be identified as a "pain reliever-fever reducer" (or the variation permitted in § 343.50(a)) and "antacid." (Products containing acetaminophen with antacid, identified in § 343.20(b)(1) in the tentative final monograph, are also being identified in the same manner.) However, the agency is not proposing to restrict acetaminophen-antacid products to dosage forms intended for ingestion as a solution because acetaminophen does not have the adverse effects on the gastrointestinal tract that are associated with aspirin (see 42 FR 35413).

The agency recognizes that in addition to a target population which uses highly buffered aspirin for solution and other aspirin with antacid products for concurrent symptoms of minor aches and pains and acid indigestion, there are consumers who also use such products just for analgesic-antipyretic use alone. The agency concludes that these products are safe and effective for both uses and that the labeling of these products should provide for use of the product for either concurrent symptoms or analgesic-antipyretic use alone. The agency notes that currently marketed products are labeled for both uses.

Therefore, the agency is proposing the following statements of indications for products containing aspirin with antacid, based on the indications for analgesic-antipyretic ingredients in § 343.50(b)(1) and the indications for antacids in § 331.30(b). New § 343.60(b)(4) for aspirin with antacid products (aspirin and antacid combinations) is being added to the tentative final monograph as follows:

(4) *For permitted combinations identified in § 343.20(b)(3).* The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") [which may be followed by: "and upset stomach associated with" (select one of the following, as appropriate: "this symptom" or "these symptoms")] and "Also may be used for the temporary relief of minor aches and pains alone" [which may be followed by one or more of the following: ("such as associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache" "the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea)"), or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)")]), ("and for the minor pain from arthritis"), and ("and to reduce fever.")]

Although the above indications apply to aspirin with antacid products, such products should not be used by persons who have persistent or recurring stomach problems, such as acid indigestion, or who have ulcers or bleeding problems, as stated in the warnings in § 343.50(c)(1)(v)(8) and (2)(v)(8). (See comment 31 above.)

The agency is proposing that products containing acetaminophen with antacid be identified according to §§ 331.30 and 343.50 and bear labeling indications in accordance with § 343.60(b)(2). The agency believes that the proposed labeling for acetaminophen with antacid products and for aspirin with antacid products (including highly buffered aspirin for solution products) provides for the safe and effective OTC use of both combinations.

The agency is aware that the Antacid Panel recommended that any generally recognized as safe and effective analgesic ingredient could be combined with any antacid for concurrent symptoms (38 FR 8724) and that this recommendation is included in the final monograph for OTC antacid drug products (21 CFR 331.15(b)). However, this recommendation was based on data submitted for an aspirin-antacid combination product and an acetaminophen-antacid combination product both in forms intended for ingestion as a solution. No data were submitted to either the Antacid Panel or the Internal Analgesic Panel to support combinations of other Category I analgesics, especially non-aspirin salicylates, e.g., magnesium salicylate with an antacid. Because there are not sufficient data to support such combinations and because of a lack of evidence of the marketing of these combinations, the agency is not proposing to include combinations of non-aspirin salicylates (i.e., choline salicylate, magnesium salicylate, and sodium salicylate) and carbaspirin calcium with antacids in this tentative final monograph and is classifying such combinations in Category III. The final monograph for OTC antacid drug products currently provides for antacid-analgesic combinations marketed in a form intended for ingestion as a solution only (21 CFR 331.15(b)). That monograph, which was developed many years ago, provides for an antacid to be combined with any generally recognized as safe and effective analgesic ingredient(s). However, as discussed above, certain possible combinations have never been marketed and lack supporting data. Therefore, elsewhere in this issue of the Federal Register, the agency is proposing to amend the antacid final monograph so that it and the internal analgesic monograph will be consistent.

References

(1) Needham, C.D., et al., "Aspirin and Alcohol in Gastrointestinal Haemorrhage," *Gut*, 12:819–821, 1971.

(2) Jennings, G.H., "Causal Influences in Haematemesis and Melaena," *Gut*, 6:1–13, 1965.

(3) Astley, C.E., "Gastritis, Aspirin, and Alcohol" (letter to the editor), *British Medical Journal*, 4:484, 1967.

(4) Mould, G., "Faecal Blood-Loss after Sodium Acetylsalicylate Taken with Alcohol" (letter to the editor), *Lancet*, 1:1268, 1969.

(5) Croft, D.N., "Gastritis," *British Medical Journal*, 4:164–166, 1967.

(6) Innes, J.A., M.J. Ford, and J.F. Munro, "Gastro-Intestinal Haemorrhage Following

Ingestion of 'Alka-Seltzer,'" *Scottish Medical Journal*, 25:105–106, 1980.

48. One comment asserted that the terms "extra strength" and "extra pain relief" should be allowed in describing products containing 500 mg acetaminophen. The comment contended that these terms are justified because 1,000 mg (two 500-mg tablets) acetaminophen provides greater pain relief than 650 mg acetaminophen (two 325-mg tablets). Other comments opposed the use of such labeling claims. One comment proposed that the labeling of products containing nonstandard dosage units contain a statement denying the therapeutic advantage of products labeled in this manner.

The agency recognizes, as the Panel did, that the OTC drug market currently includes many different products containing analgesic-antipyretic drugs, either as single active ingredients or in combination with other active ingredients. Most of these products contain either aspirin or acetaminophen in varying amounts of active ingredients(s) per dosage unit.

The Panel believed that the availability of products containing different amounts of aspirin per dosage unit is confusing to consumers and encouraged the current use of claims such as "higher levels of pain reliever." To inform the consumer more fully of the contents and therapeutic capabilities of these products and to minimize confusion, the Panel recommended that products be clearly labeled as to the amount of active ingredient per dosage unit. The Panel further recommended the establishment of standard dosage units for aspirin, acetaminophen, and sodium salicylate (42 FR 35357). Based on these criteria, the Panel proposed that these ingredients and comparable analgesic drugs be labeled as containing either a "standard" or "nonstandard" dosage unit. As discussed in comment 53 below, the agency will not require the terms "standard" and "nonstandard" in labeling.

The Panel did not specifically address the terms "extra strength" and "extra pain relief," but did recommend a wide dosage range for which OTC analgesic-antipyretic drug products are safe and effective. The Panel recommended a 325-mg minimum effective dose, but also recognized 650 mg as the usual single dose. Furthermore, the Panel found that there may be circumstances when more than the usual single dose may be needed for an adequate effect, provided the daily dosage does not exceed 4,000 mg in a 24-hour period (42 FR 35360), and thus recommended OTC dosage ranges of 325 to 650 mg every 4 hours, more than 325 mg to 500 mg every 3 hours, or 842 to 1,000 mg every 6 hours.

In general, the agency concurs with the Panel's recommended dosage schedule, which is flexible and which provides for a wide dosage range per dosage unit. (See comment 53 below for further discussion.) Terms such as "extra strength" may be helpful to consumers by alerting them to the fact that products bearing such labeling may not necessarily contain the quantity of analgesic-antipyretic that is contained in other products they have purchased. However, the agency tentatively concludes that "extra strength," "maximum strength," "extra pain relief," and similar terms that are only peripherally related to product safety and effectiveness are outside the scope of the OTC drug review. Therefore, these terms will not be included in labeling required by the monograph, but may be used elsewhere in labeling, but not intermixed with monograph labeling, subject to the provisions of section 502 of the act. The agency encourages drug manufacturers voluntarily to provide consumers with an explanation of terms such as "extra strength" and "maximum strength" when they are used in labeling.

49. One comment requested that the professional labeling recommended in § 343.80 be amended to include an indication for the use of aspirin for transient ischemic attacks. Another comment requested that buffered aspirin also be included in this indication. The comments presented data to support their requests (Ref. 1).

A transient ischemic attack is a sudden onset of a focal neurologic dysfunction that may precede a stroke. It affects the brain or retina and clears after a period lasting from a few seconds up to 24 hours. The data submitted by the comments included two multicenter clinical studies as follows: a 37-month trial conducted by Fields et al. (Ref. 2) and a 55-month trial conducted by The Canadian Cooperative Study Group (Ref. 3).

The study by Fields et al. was a randomized, double-blind trial comparing aspirin with placebo in 178 patients to determine the incidence of subsequent transient ischemic attack, death, cerebral infarction, or retinal infarction. Only persons with episodes of monocular blindness or hemispheric-type transient ischemic attacks were eligible for admission to the study. Persons with symptoms in the carotid area were included, and those with only vertebrobasilar symptoms were excluded. Another requirement was that the most recent transient ischemic attack had occurred not more than 3 months prior to randomization. The absolute endpoints studied were mortality, retinal infarctions, and cerebral infarctions.

The analysis of the absolute endpoints, i.e., death or cerebral or retinal infarction, failed to show a statistically significant differential between aspirin and placebo. However, because the primary objective of the study was to determine whether aspirin would result in a reduction of transient ischemic attacks, a second class of endpoints was used to evaluate the patients' experience during the first 6 months of follow-up (after randomization). Endpoints included not only infarctions (cerebral or retinal) but also the number of transient ischemic attacks reported. When the absolute endpoints were coupled with the occurrence of transient ischemic attack in the first 6 months of follow-up, there was a statistically significant differential (p 0.01) in favor of aspirin. When the patients were separately grouped according to whether they had a single carotid transient ischemic attack or multiple attacks before admission to the study, a life table analysis of absolute endpoints revealed a statistical significance in favor of aspirin within the group of patients with multiple attacks. When the occurrence of carotid transient ischemic attacks during the first 6 months of follow-up was also taken into consideration, analysis of patients who had single or multiple transient ischemic attacks revealed a statistically significant differential in favor of aspirin.

The study conducted by the Canadian Cooperative Study Group was a randomized, four-treatment, double-blind trial to determine whether aspirin or sulfinpyrazone, singly or in combination, was superior to placebo in preventing transient ischemic attacks, stroke, or death in patients afflicted with transient ischemic attacks or partial nonprogressing stroke in either carotid or vertebral territory (Ref. 3). Approximately 65 percent of the 585 subjects had symptoms suggesting brain ischemia in the area supplied by the carotid artery; 25 percent of the subjects were affected in the area supplied by the vertebrobasilar artery; and 10 percent of the subjects had both the vertebrobasilar and carotid arteries affected. Patients with hemodynamic (pertaining to the movements involved in the circulation of the blood) or cardiac causes were excluded from the study. The average period of followup was 26 months. The compliance rate was 92 percent.

Three endpoints were assessed in the study: Transient ischemic attack, stroke, and death. If any of these endpoints occurred by the end of the trial, or within 6 months of withdrawal where treatment had been terminated, they were counted against their randomly assigned treatment regimen. None of the 3 drug treatment groups was significantly different from the placebo treatment group for any endpoint, but when the 2 treatment groups taking aspirin (i.e., aspirin alone and aspirin with sulfinpyrazone) were compared with the two groups that were not taking aspirin (i.e., the groups taking sulfinpyrazone alone or placebo) for the combined endpoints of stroke and death, the reduction with aspirin was 31 percent ($p < 0.05$). In subset analysis, the benefit from aspirin therapy was confined to males, with a 48-percent reduction in stroke and death ($p < 0.005$). There was no significant benefit in females in either treatment category.

Based upon the data described above, the agency's Peripheral and Central Nervous System (CNS) Drugs Advisory Committee concluded that there is evidence that aspirin is safe and effective for reducing the risk of recurrent transient ischemic attacks or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli (Refs. 2, 3, and 4). In concluding that aspirin is safe and effective in reducing these risks in males, the Committee recommended a dosage of 1,300 mg aspirin per day in divided doses of 650 mg twice a day or 325 mg four times a day.

Studies were submitted on the absorption characteristics of buffered aspirin and plain aspirin products (Refs. 5 and 6). Nayak et al. (Ref. 5) conducted three blinded studies (A, B, and C) on the effect of antacids on aspirin dissolution and bioavailability. The 12 normal adult subjects (8 male, 4 female) abstained from using any medication 1 week before and during the studies.

Study A was conducted to determine the absorption characteristics of four aspirin formulations with different buffering capacity and in vitro dissolution profile. Each subject abstained from solid food and liquids, except water, from midnight of each study day. The subjects were randomly divided into four equal groups assigned to the rows of a selected 4 x 4 Latin square. On each of the test days, which were 1 week apart, a single dose (2 tablets) of each of the following formulations was given: 325 mg aspirin; 325 mg aspirin with 150 mg aluminum hydroxide gel and 150 mg magnesium hydroxide; 325 mg aspirin with 75 mg aluminum hydroxide gel and 75 mg magnesium hydroxide; and 325 mg aspirin with 50 mg aluminum glycinate and 100 mg magnesium carbonate. A pretest blood sample was collected, and each subject was given a single dose of the formulations with 200 mL water.

Blood samples were collected at various intervals; the plasma was separated and frozen before being analyzed. Results were expressed as the total salicylate concentration in salicylic acid equivalents, and a pharmacokinetic analysis of data was performed. The results showed that the buffered formulations produced significantly higher peak concentrations of plasma salicylate than the unbuffered formulation. However, a comparison of the area-under-curve values showed no statistically significant difference among formulations.

Study B was conducted to assess the effect that doubling the aspirin and antacid dose would have on the absorption of aspirin. The subjects and methods were identical to study A except that each subject was given a single dose of four tablets containing 325 mg aspirin, 150 mg aluminum hydroxide gel, and 150 mg magnesium hydroxide per tablet. A pharmacokinetic analysis of data was performed.

In study C, 2 hours after a meal of 1 cup of dry cereal, 8 oz of whole milk, 6 oz of orange juice, sugar, and 1 cup of coffee or tea, three male subjects received four tablets of the same formulation used in study B (Ref. 5). The subjects swallowed the tablets with 200 mL water. The blood sampling and analysis were the same as in study A, except that blood was collected without anticoagulant and processed for serum.

The results of studies B and C showed that the concentration-time profile and the bioavailability were similar in both studies. Thus, there was no evidence of a lower or erratic absorption of aspirin due to the antacids used as compared with unbuffered aspirin.

A study was conducted to determine whether the aspirin in a commercial buffered aspirin product containing 325 mg aspirin and 150 mg magnesium-aluminum hydroxide was as effective as 325 mg plain aspirin in inhibiting platelet aggregation in vitro (Ref. 6). The methodology was collagen-induced aggregation of guinea pig or human platelets (in vitro). Separate solutions of aspirin and the buffered aspirin product were prepared using sterile saline solution. Each solution contained 3.25 mg aspirin per mL, equivalent to a molar aspirin concentration of 1.8×10^{-2}. Subsequent dilutions were used at a log concentration ratio of 1.5. Nonfasted male guinea pigs weighing 300 to 500 g were used throughout the study. When human platelets were used, they were separated and handled in the same way as those collected from guinea pigs.

Platelet aggregation assays were conducted, and the data were quantified by calculating area-under-curve values for each dilution. Aspirin and the buffered aspirin product were first compared in an experiment to find a dose range.

The results showed that both the plain aspirin and the buffered aspirin product would produce dose-related inhibitory effects on the aggregation of guinea pig platelets in the range of 1.8×10^{-4} to 1.8×10^{-5} molar concentration. The concentration for 50 percent inhibition (IC_{50}) was found to be 1.3×10^{-4} molar for the aspirin in the plain aspirin product. In the buffered aspirin product the IC_{50} was found to be 1.4×10^{-4} molar. The investigators concluded that the similarity of the IC_{50} values indicates there is no difference between the effect of plain aspirin and the effect of the buffered aspirin product on platelet aggregation. The IC_{50} values for aspirin and the buffered aspirin product on human platelets (1.4×10^{-4} and 1.3×10^{-4}, respectively) were close to those found for guinea pig platelets. The slopes of the respective regression lines were similar, indicating no specific differences.

The investigators concluded that plain aspirin and the buffered aspirin product are equally effective in inhibiting collagen-induced aggregation of both guinea pig and human platelets in vitro and that the buffered aspirin product would be as useful as plain aspirin in the prevention of transient ischemic attacks.

Based upon the Peripheral and CNS Drugs Advisory Committee's recommendation on aspirin and transient ischemic attacks and the agency's review of the data submitted to show that buffered aspirin would be expected to have similar effects, the agency concludes that both aspirin and buffered aspirin can be used for reducing the risk of recurrent transient ischemic attacks or stroke in males. This use of aspirin and buffered aspirin is being proposed for incorporation into the professional labeling section of the tentative final monograph, with the recommended dosage of 1,300 mg aspirin per day in divided doses of 650 mg twice a day or 325 mg four times a day. The agency believes that sodium-containing buffered aspirin should not be used for this purpose because the chronic ingestion of sodium is ill-advised in this patient population.

The agency also points out that aspirin or buffered aspirin without sodium is not indicated in all forms of sudden onset of focal neurologic dysfunction simulating transient ischemic attacks. Also, the effects of concurrent administration of therapeutic amounts of antacids on the absorption and the elimination of aspirin must be considered, but the current literature contains minimal information on these effects.

Levy et al. (Ref. 7) conducted a study on three children with rheumatic fever to determine whether serum salicylate concentrations are affected by an antacid containing aluminum and magnesium hydroxide. Aspirin bioavailability (completeness of absorption) was estimated from the amount of total salicylate excreted in the children's urine over a 2-hour period, with urine specimens collected during the antacid and control periods. The investigators found that the estimated daily excretion was in reasonably good agreement with the daily dose and did not decrease during antacid administration.

Levy et al. (Ref. 7) also investigated the effect of an antacid containing aluminum and magnesium hydroxide on the bioavailability of aspirin in five healthy adult males. Each subject received two 325-mg tablets of aspirin 1 hour after a breakfast of 28 g corn flakes and 500 mL milk. The tablets were swallowed whole with 50 mL water. Two of the subjects first received only aspirin; the other three were given 20 mL aluminum and magnesium hydroxide suspension with 50 mL water immediately after the aspirin was ingested. No food or coffee was permitted for 4 hours, and each subject's urine was collected periodically for 48 hours.

About 1 week later, crossover experiments compared the percentage of salicylate recovered in each subject's urine with aspirin given alone to the percentage recovered when the aspirin-antacid was given. Results (expressed as total salicylate recovered) showed that the antacid product containing aluminum and magnesium hydroxide had no apparent effect on aspirin absorption.

In addition, while reviewing data on the use of aspirin for myocardial infarction, the agency identified certain information that it considers pertinent to the use of aspirin for the prevention of transient ischemic attacks (see comment 50 below). In the Aspirin Myocardial Infarction Study (AMIS) (Ref. 8), the dosage of 1,000 mg per day of aspirin was associated with small increases in blood pressure, blood urea nitrogen, and serum uric acid levels. This dosage was also associated with increased incidences of gastrointestinal symptoms including stomach pain, heartburn, nausea and/or vomiting, as well as gross gastrointestinal bleeding. Because the dosage of aspirin proposed for the prevention of transient ischemic attacks is 1,300 mg, the agency believes that this information should be included in the proposed professional labeling for aspirin for transient ischemic attacks.

References

(1) Comment Nos. SUP005, SUP011, and CP, Docket No. 77N-0094, Dockets Management Branch.

(2) Fields, W.S., et al., "Controlled Trial of Aspirin in Cerebral Ischemia," *Stroke* 8:301-316, 1977.

(3) The Canadian Cooperative Study Group, "A Randomized Trial of Aspirin and Sulfinpyrazone in Threatened Stroke," *New England Journal of Medicine*, 299:53-59, 1978.

(4) Minutes of the FDA Peripheral and CNS Drugs Advisory Committee, August 28, 1979, included in OTC Volume 03BTFM.

(5) Nayak, R.K., et al., "Effect of Antacids on Aspirin Dissolution and Bioavailability," *Journal of Pharmacokinetics and Biopharmaceutics*, 5:597-613, 1977.

(6) W.H. Rorer, Inc., Research Division, "The Inhibition by Ascriptine of Collagen-Induced Aggregation of Guinea Pig and Human Platelets in Vitro," unpublished report in Vol. 2 of Citizen's Petition (CP), Docket No. 77N-0094, Dockets Management Branch.

(7) Levy, G., et al., "Decreased Serum Salicylate Concentrations in Children with Rheumatic Fever Treated with Antacid," *New England Journal of Medicine*, 293:323-325, 1975.

(8) Aspirin Myocardial Infarction Study Research Group, "A Randomized, Controlled Trial of Aspirin in Persons Recovered from Myocardial Infarction," *Journal of the American Medical Association*, 243:661-699, 1980.

Based upon the above discussion, the agency is proposing in § 343.80(b) the following indications, precautions, and dosage in the professional labeling:

For products containing aspirin identified in § 343.10(b) or permitted combinations identified in § 343.20(b)(4) except those containing sodium. The labeling states, under the heading "ASPIRIN FOR TRANSIENT ISCHEMIC ATTACKS," the following:

Indication:

For reducing the risk of recurrent transient ischemic attacks (TIA's) or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli. There is inadequate evidence that aspirin or buffered aspirin is effective in reducing TIA's in women at the recommended dosage. There is no evidence that aspirin or buffered aspirin is of benefit in the treatment of completed strokes in men or women.

Clinical Trials:

The indication is supported by the results of a Canadian study [1] in which 585 patients with threatened stroke were followed in a randomized clinical trial for an average of 26 months to determine whether aspirin or sulfinpyrazone, singly or in combination, was superior to placebo in preventing transient ischemic attacks, stroke, or death. The study showed that, although sulfinpyrazone had no statistically significant effect, aspirin reduced the risk of continuing transient ischemic attacks, stroke, or death by 19 percent and reduced the risk of stroke or death by 31 percent. Another aspirin study carried out in the United States with 178 patients, showed a statistically significant number of "favorable outcomes," including reduced transient ischemic attacks, stroke, and death.

Precautions:

Patients presenting with signs and symptoms of TIA's should have a complete medical and neurologic evaluation. Consideration should be given to other disorders that resemble TIA's. Attention should be given to risk factors: It is important to evaluate and treat, if appropriate, other diseases associated with TIA's and stroke, such as hypertension and diabetes.

Concurrent administration of absorbable antacids at therapeutic doses may increase the clearance of salicylates in some individuals. The concurrent administration of nonabsorbable antacids may alter the rate of absorption of aspirin, thereby resulting in a decreased acetylsalicylic acid/salicylate ratio in plasma. The clinical significance of these decreases in available aspirin is unknown.

Aspirin at dosages of 1,000 milligrams per day has been associated with small increases in blood pressure, blood urea nitrogen, and serum uric acid levels. It is recommended that patients placed on long-term aspirin treatment be seen at regular intervals to assess changes in these measurements.

Adverse Reactions:

At dosages of 1,000 milligrams or higher of aspirin per day, gastrointestinal side effects include stomach pain, heartburn, nausea and/or vomiting, as well as increased rates of gross gastrointestinal bleeding. (Other applicable warnings related to the use of aspirin as described in § 343.50(c) may also be included here.)

Dosage and Administration:

Adult oral dosage for men is 1,300 milligrams a day, in divided doses of 650 milligrams twice a day or 325 milligrams four times a day.

References

(1) The Canadian Cooperative Study Group, "A Randomized Trial of Aspirin and Sulfinpyrazone in Threatened Stroke," *New England Journal of Medicine*, 299:53-59, 1978.

(2) Fields, W.S., et al., "Controlled Trial of Aspirin in Cerebral Ischemia," *Stroke*, 8:301-316, 1977.

50. One comment submitted data (Ref. 1) and requested that the professional labeling recommended in § 343.80 be

expanded to include an indication for the use of aspirin in the prophylaxis of secondary myocardial infarction. Another comment submitted data (Ref. 2) and requested the agency to issue professional labeling guidelines that provide for the use of highly buffered aspirin in solution to prevent myocardial infarction in men with unstable angina.

The agency has reviewed the submitted data and determined that aspirin is effective in reducing the risk of death and/or non-fatal myocardial infarction in patients with a previous infarction or unstable angina pectoris. The agency evaluated six secondary prevention trials (Refs. 3 through 8) and one controlled clinical trial of unstable angina (Ref. 9). Although none of the six secondary prevention trials individually showed a significant aspirin effect on mortality, the pooled results did show a moderately impressive statistically significant reduction in the occurrence of death and/or non-fatal myocardial infarction. Five of the six secondary prevention trials showed a favorable trend. Two of the individual studies showed a significant effect, and two others showed a near significant effect ($p=0.06$, $p=0.08$) on the combined endpoint of non-fatal infarction and/or death, as well as on non-fatal infarction alone. The pooled results showed a highly significant aspirin treatment effect on the combined or non-fatal infarction endpoint. The post-infarction and unstable angina trials, while studies of different diseases, mutually support each other by showing effects on the same endpoint. The trials also provide pertinent dosing information.

Five of the six secondary prevention trials used doses of 1,000 mg per day or more; one of these trials and the unstable angina trial used about 300 mg per day. The latter two trials, along with considerable pharmacologic evidence that platelet-induced thrombogenesis can be reduced by doses near 300 mg and the expectation that gastrointestinal bleeding would likely be less prominent at lower dosages, have led the agency to conclude that 300 mg (or a conventional 325 mg dose) of aspirin per day is effective for the prevention of myocardial infarction in patients with a previous myocardial infarction or unstable angina.

In the secondary prevention trials, aspirin treatment was started at intervals after the onset of acute myocardial infarction varying from less than three days to more than five years and continued for periods of from less than one year to four years. Treatment within a week of onset of myocardial infarction was not shown to be beneficial in the cases presenting with acute infarction in the unstable angina trial. The data did show beneficial trends for stronger effects in the first six months after acute infarction and for the first two years after starting treatment. However, these trends were not well enough established to justify limiting treatment to these intervals. Due to this uncertainty, the labeling that the agency is proposing does not include any specific recommendation regarding when to start or stop aspirin treatment.

Most of the subjects in the secondary prevention trials and all of those in the unstable angina trials were male. Due to the small numbers of females in the studies, the use of aspirin for this indication in women cannot be supported by available data. However, the agency does not believe that use in women is necessarily unreasonable and the professional labeling that the agency is proposing does not discourage such use, but simply notes the limitation on the number of females in the clinical trials.

In the Aspirin Myocardial Infarction Study (AMIS) (Ref. 3), the aspirin-treated group showed a small increase in blood pressure after adjustment for baseline pressure. Similar findings for other United States aspirin trials of secondary prevention were also found. While these blood pressure elevations were clinically small, the agency believes that this finding should be included in the labeling. The agency also believes that it should be kept in mind that only about 10 percent of the subjects were hypertensive at baseline and that the blood pressure eligibility restrictions in these trials were such that severely hypertensive subjects were not entered (Refs. 4 and 5). Aspirin treated groups in both the AMIS trial and the United States aspirin studies showed small but definite increases in blood urea nitrogen and uric acid; thus, the agency concludes that during the course of long-term aspirin therapy users of this drug should be monitored regularly to assess changes in these measurements.

Based on the data from the unstable angina trial of Lewis et al. (Ref. 9), which used one 325 mg dose of aspirin in a highly buffered solution, the agency has concluded that highly buffered aspirin for solution (aspirin/antacid combination (see comment 76 below)) as well as buffered aspirin in a solid dosage form is safe and effective to reduce the risk of death and/or non-fatal myocardial infarction in patients with a previous myocardial infarction or unstable angina. However, the agency believes that sodium intake should be considered in this patient population and has included a statement concerning the amount of sodium in the aspirin/antacid combination in the Lewis trial (Ref. 9) and how much this amount of sodium adds to the intake suggested as appropriate for the dietary treatment of essential hypertension in the "1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (Ref. 10).

In conclusion, the agency is proposing that the professional labeling section of the tentative final monograph (i.e., information provided to health professionals only, and not to the general public) should include aspirin for the indication, "to reduce the risk of death and/or non-fatal myocardial infarction in patients with a previous myocardial infarction or unstable angina pectoris." The agency is proposing in § 343.80(c) the following professional labeling:

For products containing aspirin identified in § 343.10(a) or permitted combinations identified in § 343.20(b),(3) and (4). The labeling states, under the heading "ASPIRIN FOR MYOCARDIAL INFARCTION," the following: *Indication:*

Aspirin is indicated to reduce the risk of death and/or non-fatal myocardial infarction in patients with a previous infarction or unstable angina pectoris. *Clinical Trials:*

The indication is supported by the results of six large, randomized multicenter, placebo-controlled studies involving 10,816, predominantly male, post-myocardial infarction (MI) patients and one randomized placebo-controlled study of 1,266 men with unstable angina [1-7]. Therapy with aspirin was begun at intervals after the onset of acute MI varying from less than 3 days to more than 5 years and continued for periods of from less than 1 year to 4 years. In the unstable angina study, treatment was started within 1 month after the onset of unstable angina and continued for 12 weeks, and patients with complicating conditions such as congestive heart failure were not included in the study.

Aspirin therapy in MI patients was associated with about a 20-percent reduction in the risk of subsequent death and/or non-fatal reinfarction, a median absolute decrease of 3 percent from the 12- to 22-percent event rates in the placebo groups. In aspirin-treated unstable angina patients the reduction in risk was about 50 percent, a reduction in the event rate of 5 percent from the 10-percent rate in the placebo group over the 12-weeks of the study.

Daily dosage of aspirin in the post-myocardial infarction studies was 300 milligrams in one study and 900 to 1,500 milligrams in 5 studies. A dose of 325 milligrams was used in the study of unstable angina.

Adverse Reactions:

Gastrointestinal Reactions:

Doses of 1,000 milligrams per day of aspirin caused gastrointestinal symptoms and bleeding that in some cases were clinically

significant. In the largest post-infarction study (the Aspirin Myocardial Infarction Study (AMIS) with 4,500 people), the percentage incidences of gastrointestinal symptoms for the aspirin (1,000 milligrams of a standard, solid-tablet formulation) and placebo-treated subjects, respectively, were: stomach pain (14.5 percent; 4.4 percent); heartburn (11.9 percent; 4.8 percent); nausea and/or vomiting (7.6 percent; 2.1 percent); hospitalization for gastrointestinal disorder (4.8 percent; 3.5 percent). In the AMIS and other trials, aspirin-treated patients had increased rates of gross gastrointestinal bleeding. Symptoms and signs of gastrointestinal irritation were not significantly increased in subjects treated for unstable angina with buffered aspirin in solution.

(Other applicable warnings related to the use of aspirin as described in § 343.50(c) may also be included here.)

Cardiovascular and Biochemical:

In the AMIS trial, the dosage of 1,000 milligrams per day of aspirin was associated with small increases in systolic blood pressure (BP) (average 1.5 to 2.1 millimeters) and diastolic BP (0.5 to 0.6 millimeters), depending upon whether maximal or last available readings were used. Blood urea nitrogen and uric acid levels were also increased, but by less than 1.0 milligram percent.

Subjects with marked hypertension or renal insufficiency had been excluded from the trial so that the clinical importance of these observations for such subjects or for any subjects treated over more prolonged periods is not known. It is recommended that patients placed on long-term aspirin treatment, even at doses of 300 milligrams per day, be seen at regular intervals to assess changes in these measurements.

Sodium in Buffered Aspirin for Solution Formulations:

One tablet daily of buffered aspirin in solution adds 553 milligrams of sodium to that in the diet and may not be tolerated by patients with active sodium-retaining states such as congestive heart or renal failure. This amount of sodium adds about 30 percent to the 70- to 90-millequivalents intake suggested as appropriate for dietary treatment of essential hypertension in the "1964 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure".[8]

Dosage and Administration:

Although most of the studies used dosages exceeding 300 milligrams, 2 trials used only 300 milligrams and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 milligrams or a conventional 325 milligram aspirin dose is a reasonable, routine dose that would minimize gastrointestinal adverse reactions. This use of aspirin applies to both solid, oral dosage forms (buffered and plain aspirin) and buffered aspirin in solution.

References

(1) Elwood, P.C., et al., "A Randomized Controlled Trial of Acetylsalicylic Acid in the Secondary Prevention of Mortality from Myocardial Infarction," *British Medical Journal*, 1:436-440, 1974.

(2) The Coronary Drug Project Research Group, "Aspirin in Coronary Heart Disease," *Journal of Chronic Diseases*, 29:625-642, 1976.

(3) Breddin K., et al., "Secondary Prevention of Myocardial Infarction: A Comparison of Acetylsalicylic Acid, Phenprocoumon or Placebo," *Homeostasis*, 470:263-268, 1979.

(4) Aspirin Myocardial Infarction Study Research Group, "A Randomized, Controlled Trial of Aspirin in Persons Recovered from Myocardial Infarction," *Journal of the American Medical Association*, 243:661-669, 1980.

(5) Elwood, P.C., and P.M. Sweetnam, "Aspirin and Secondary Mortality after Myocardial Infarction," *Lancet*, II:1313-1315, December 22-29, 1979.

(6) The Persantine-Aspirin Reinfarction Study Research Group, "Persantine and Aspirin in Coronary Heart Disease," *Circulation*, 62:449-461, 1980.

(7) Lewis, H.D., et al., "Protective Effects of Aspirin Against Acute Myocardial Infarction and Death in Men with Unstable Angina. Results of a Veterans Administration Cooperative Study," *New England Journal of Medicine*, 309:396-403, 1983.

(8) "1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure," United States Department of Health and Human Services and United States Public Health Service, National Institutes of Health, Publication No. NIH 84-1088, 1984.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Refs. 11 and 12).

References

(1) Comments Nos. C00108, SUP015, SUP020, and SUP026, Docket No. 77N-0094, Dockets Management Branch.

(2) Comment No. CP0005, Docket No. 77N-0094, Dockets Management Branch.

(3) Aspirin Myocardial Infarction Study Research Group, "A Randomized Controlled Trial of Aspirin in Persons Recovered From Myocardial Infarction," *Journal of the American Medical Association*, 245:661-669, 1980.

(4) The Coronary Drug Project Research Group, "Aspirin in Coronary Heart Disease," *Journal of Chronic Diseases*, 29:625-642, 1976.

(5) The Persantine-Aspirin Reinfarction Study Research Group, "Persantine and Aspirin in Coronary Heart Disease," *Circulation*, 62:449-461, 1980.

(6) Elwood, P.C., et al., "A Randomized Controlled Trial of Acetylsalicylic Acid in the Secondary Prevention of Mortality From Myocardial Infarction," *British Medical Journal*, 1:436-440, 1974.

(7) Breddin, K., et al., "Secondary Prevention of Myocardial Infarction: A Comparison of Acetylsalicylic Acid, Phenprocoumon or Placebo," *Homeostasis*, 470:263-268, 1979.

(8) Elwood, P.C., and P.M. Sweetnam, "Aspirin and Secondary Mortality After Myocardial Infarction," *Lancet*, II:1313-1315, December 22-29, 1979.

(9) Lewis, H.D., et al., "Protective Effects of Aspirin Against Acute Myocardial Infarction and Death in Men With Unstable Angina. Results of a Veterans Administration Cooperative Study," *New England Journal of Medicine*, 309:396-403, 1983.

(10) "1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure," United States Department of Health and Human Services and United States Public Health Service, National Institutes of Health, Publication No. NIH 84-1088, 1984.

(11) Letter from W.E. Gilbertson, FDA, to G.R. Pflug, Miles Laboratories, Inc., coded LET049, Docket No. 77N-0094, Dockets Management Branch.

(12) Letter from W.E. Gilbertson, FDA, to E.J. Hiross, Sterling Drug, Inc., coded LET048 Docket No. 77N-0094, Dockets Management Branch.

C. Comments on Advertising of Internal Analgesic Drug Products

51. Several comments suggested that changes be made in the quality and quantity of advertisements for OTC internal analgesic drug products to eliminate "excessive claims for minor differences in drug properties" and to reduce the likelihood of consumers being unduly persuaded or misled by such inappropriate statements. Another comment contended that consumers often do not realize from current OTC analgesic drug advertising that many of these products contain aspirin. An example of such advertising is as follows: "Contains more of the pain killer which doctors prescribe most." The comment urged that FDA require manufacturers to state in their advertising that their products contain aspirin.

The Federal Trade Commission (FTC) has the primary responsibility for regulating OTC drug advertising, and FDA has forwarded copies of the comments concerning internal analgesic advertising to the FTC for its consideration (Ref. 1). FDA does, however, have the authority to regulate OTC drug advertising that constitutes labeling under the Federal Food, Drug, and Cosmetic Act. See, e.g., *United States* v. *Article of Drug * * * B-Complex Cholinos Capsules*, 362 F.2d 923 (3d Cir. 1966); *V.E. Irons, Inc.* v. *United States*, 244 F.2d 34 (10th Cir.), *cert. denied*, 354 U.S. 923 (1957). In addition, for an OTC drug to be generally recognized as safe and effective and not misbranded, the advertising for the drug must satisfy the FDA regulations in § 330.1(d) (21 CFR 330.1(d)), which state that the advertising may prescribe, recommend, or suggest the drug's use only under the conditions stated in the labeling. If advertising for an OTC internal analgesic drug product offers the drug product for conditions not included in

the final monograph labeling, the drug product may be subject to regulatory action by FDA.

Reference

(1) Letter from L. Geismar, FDA, to W.B. Fisherow, FTC, June 18, 1981, included in OTC Volume 03BTFM.

52. Several comments asserted that the Panel extended its review beyond its charter by making statements concerning the advertising of the products under its review. The comments stated that FDA did not grant such authority in the procedures established for OTC drug advisory review panels. The comments further argued that the Panel's statements on OTC drug advertising were not only inappropriate for inclusion in the report, but also were based on inadequate information because, according to FDA procedures, data and information pertaining to advertising were not submitted to the Panel.

The OTC drug review procedures do not preclude a panel from expressing its concern about OTC drug advertising. The statements of opinion on advertising and the media were included by the Panel in its report upon the recommendation of the Panel's consumer liaison representative (Ref. 1). These statements were partly based on a transcript of the proceedings of a conference sponsored by the Federal Communications Commission and the FTC and attended by representatives of consumer advocate groups, pharmaceutical associations and manufacturers, the broadcast media, and the academic community.

The Panel discussed OTC drug advertising in its report in order to make its concerns known to the FTC, as well as to FDA.

Reference

(1) Summary Minutes of the 20th Meeting of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products, June 25, 26, and 27, 1975, incorporated in OTC Volume 030173.

D. Comments on Standard Dosage Unit and Analgesic Equivalence Value

53. Some comments supported the Panel's recommendation for standard dosage units and standard dosage schedules for all marketed OTC internal analgesic drug products containing aspirin, acetaminophen, and sodium salicylate as single ingredients. The comments stated that adopting this recommendation would benefit consumers by reducing the confusion and misuse that result from the current availability of various dosage strengths and dosage schedules of these ingredients. The comments argued that consumers are used to taking "two (325-mg) aspirin tablets" for pain relief and could ingest toxic amounts of aspirin from using dosage units larger than 325 mg. The comments maintained that dosages greater than 650 mg (two 325-mg tablets) do not provide "substantial benefit to a sufficient portion of the public" to justify making dosage unit strengths greater than 325 mg generally available.

Several comments opposed the standard and nonstandard labeling recommended by the Panel in § 343.50(d), arguing that such labeling implies differences in quality or therapeutic effect, would confuse consumers, and crowd information on the label. Several comments also opposed the concept of standard dosage units and standard dosage schedules, arguing that adopting them would deprive consumers of products with which they have been satisfied and would result in dosage changes in the labeling that may be overlooked by consumers. Some comments also argued that the concept of standard dosage unit is unsupported because various dosage levels of aspirin, acetaminophen, and sodium salicylate are safe and effective and show increasing effectiveness with increased dosages. To resolve "inconsistencies" in the dosage units and schedules, one comment recommended that the adult dosage unit for aspirin, acetaminophen, and sodium salicylate be 325 mg (standard) and 500 mg or 650 mg (nonstandard). The comment also recommended a maximum single dose of 1,000 mg for each of these ingredients with a 4-hour dosage interval and a maximum daily dose of 4,000 mg.

The agency agrees with the comments in opposition to the Panel's recommendation on standard and nonstandard labeling. The agency does not believe that use of the terms "standard" and "nonstandard" would simplify the comparison of various products containing different quantities of active ingredients or would aid consumers in selecting an OTC analgesic-antipyretic drug product. In addition, the agency is not aware that the existing manner of labeling these products has caused consumer confusion or resulted in misuse of these products. Therefore, the Panel's recommendation on standard and nonstandard labeling is not being included in this tentative final monograph.

The Panel was aware that degrees of pain and analgesic responses vary and thus provided for safe and effective OTC adult analgesic dosage ranges for aspirin and sodium salicylate of 325 to 650 mg every 4 hours, more than 325 to 500 mg every 3 hours, or 842 to 1,000 mg every 6 hours. (See the Panel's recommended § 343.10 (a) and (f).) For acetaminophen, the Panel's recommended dosage ranges were 325 to 650 mg every 4 hours, 500 mg every 3 hours, or 1,000 mg every 6 hours. (See the Panel's recommended § 343.10(b).) As stated in comment 63 below, the agency believes that it is reasonable for acetaminophen to have the same dosage and frequency of administration as aspirin. The agency is revising the dosage schedule for acetaminophen to conform to that of aspirin. In addition, the dosage of "more than" 325 mg to 500 mg every 3 hours is being restated as 325 mg to 500 mg every 3 hours to include the 325-mg minimal effective dose. Likewise, in consideration of the various analgesic dosage unit strengths currently being marketed, the agency is proposing that the dosage of 842 to 1,000 mg every 6 hours be revised to 650 to 1,000 mg every 6 hours to include the maximum recommended dose to be taken every 4 hours (i.e., 650 mg) as a minimum dose taken every 6 hours. The agency invites specific comment on this proposal.

Based upon the above conclusions and dosage recommendations, the dosage schedules for aspirin, acetaminophen, and sodium salicylate recommended by the Panel in § 343.10 (a), (b), and (f) are being revised to eliminate the concepts of "standard" and "nonstandard" schedules and are being combined under § 343.50(d)(2). The Panel's definitions of standard dosage units for these ingredients in § 343.3 (c), (m), and (p) are not being proposed in this tentative final monograph.

The agency notes that the Panel discussed a maximum initial single dose of 975 mg (15 grains (gr)) (three dosage units of 325 mg each) in a 4-hour dosing regimen (43 FR 35361) and recommended this loading dose for aspirin, acetaminophen, and sodium salicylate (§ 343.12 (a)(ii), (b)(ii), and (f)(ii)). The agency is not proposing a loading dose for these ingredients because it believes that such a provision may confuse consumers and lead to repeated dosing of 975 mg every 4 hours instead of 325 mg to 650 mg every 4 hours. For reasons stated in comments 62 and 63 below, the agency is not proposing an OTC dose of 975 mg (15 gr) or 1,000 mg every 4 hours.

54. Two comments objected to the standard dosage unit concept because it is not applicable to liquid products or a product containing aspirin in a gum base. One comment argued that it is inappropriate to use the standard

dosage unit concept for certain liquids that contain combinations of analgesic ingredients and cough/cold ingredients. The other comment, noting that the advance notice of proposed rulemaking did not provide for a nonstandard dosage unit of 227.5 mg (3.5 gr) aspirin, requested that §§ 343.10(a) and 343.12(a) be expanded to include this nonstandard dosage unit, which is identical to that of the gum base product.

As stated in comment 53 above, the agency is not adopting the Panel's recommendation for a standard dosage unit of 325 mg for OTC analgesic drug products. However, the dosage schedules of all OTC internal analgesic drug products, including liquid and gum base dosage forms, will have to comply with the final monograph when it is published. (See comments 53 above and 58 below.)

55. One comment stated that in establishing standard and usual doses the agency should not limit manufacturers to the exact metric equivalent of 10 gr, or its approximation, 650 mg. The comment pointed out that because the "United States Pharmacopeia" (U.S.P) (Ref. 1) recognizes 600 mg as the approximate metric equivalent of 10 gr, products containing either 600 or 650 mg (or the exact equivalent of 643 mg) should be allowed to use the term "usual dose."

Although the U.S.P recognizes 600 mg as an approximate equivalent to 10 gr (Ref. 2), the agency is not including the comment's suggestion that quantities other than 650 mg be equivalent to 10 gr because it agrees with the Panel's recommendation that the system of weight measurement for OTC internal analgesic drug products should be based on 1 gr being equivalent to 65 mg (42 FR 35357.)

The "usual dose" of OTC analgesic-antipyretic drugs is any of the doses that conform with the dosages specified in this tentative final monograph in the section on directions. However, the agency is not allowing use of the term "usual dose" as a descriptive term for the same reasons that it did not adopt the use of the terms "standard" and "nonstandard." (See comment 53 above.)

References

(1) "United States Pharmacopeia XX—National Formulary XV." United States Pharmacopeial Convention, Inc., Rockville, MD (inside back cover), 1980.

(2) "United States Pharmacopeia XXI—National Formulary XVI, United States Pharmacopeial Convention, Inc., Rockville, MD (inside back cover), 1985.

56. Several comments opposed the adoption of the Panel's recommended labeling statement in § 343.50(e) on analgesic equivalence value for calcium carbaspirin, choline salicylate, and magnesium salicylate. The comments contended that such labeling would crowd the required information on the label, confuse consumers, and imply that one product is more, or less, effective than another when in fact all products included in the monograph are safe and effective. Other comments, although not opposed to analgesic equivalence labeling, stated that such labeling is confusing and suggested alrernative labeling statements.

The agency agrees with the comments that such statements could be misleading to consumers. All products that meet the specifications of the monograph are safe and effective. Therefore, the agency is not adopting the analgesic equivalence value labeling statements recommended by the Panel, and § 343.50(e), statement on analgesic equivalence value, and § 343.3 (a), (i), and (o), definitions of acetaminophen, aspirin, and sodium salicylate equivalence values, are not being included in this tentative final monograph.

57. One comment argued that the 325-mg (5 gr) unit dose restriction recommended by the Panel was not appropriate for analgesic powders. The comment contended that analgesic powders represent a dosage form in which the dosage and dosage unit are equivalent. For example, one powder envelope usually contains the equivalent of two tablets of "standard" aspirin. Because the Panel allowed an initial maximum dosage of 1,000 mg and also a 1,000-mg dosage every 6 hours, the comment requested that the agency permit a dosage of 1,000 mg or less in one powder envelope, provided the Panel's dosage schedule is followed and the total daily dose does not exceed 4,000 mg.

As discussed in comment 53 above, the agency is proposing not to adopt the Panel's recommendation for a specific adult dosage unit strength. Thus, OTC analgesic-antipyretic powders may be formulated with a 1,000-mg dosage unit strength per powder envelope. However, the dosage schedules of analgesic-antipyretic powders must be in conformance with the final monograph.

E. Comments on Recommended Dosage Schedules

58. One comment urged that the Panel's recommendation in §§ 343.10(a)(2) and 343.12(a)(2) be revised by increasing the children's dosage unit for aspirin products from 80 mg (1.23 gr) to 81 mg (1.25 gr) and revising the children's dosage schedule accordingly. The comment contended that the 80-mg dosage unit is unavailable in aspirin products and that conversion to an 80-mg dosage unit would invalidate all currently available stability data for children's aspirin products. The comment argued that the availability of the 81-mg (1¼ gr) dosage unit is recognized in §§ 201.314(c) (1) and (2) (21 CFR 201.314(c) (1) and (2)) and in the USP (Ref. 1). The comment concluded that a dosage schedule based on the 81-mg dosage unit is consistent with the dosage schedules for aspirin in §§ 343.10(a)(1)(i) and 343.12(a)(1)(i) because 325 mg is a more accurate multiple of 81 mg than of 80 mg.

The agency acknowledges that there has been longstanding acceptance of the 81-mg (1¼ gr) children's dosage unit for aspirin and agrees with the comment that it should be retained. Children's acetaminophen products are marketed in an 80-mg dosage unit strength, but the difference between 80-mg and 81-mg dosage unit strengths is of no therapeutic consequence. Thus, the agency believes that the children's dosage unit for aspirin, acetaminophen, and sodium salicylate should be either 80 mg or 81 mg, and the dosage schedule for children's products is being revised accordingly.

In addition, the agency notes that the recommended dose of aspirin, acetaminophen, and sodium salicylate for children 6 to 9 years of age is 325 mg (or 320 mg when four 80-mg dosage units are used and 324 mg when four 81-mg dosage units are used). Because this dose (i.e., 325 mg) is also the minimal effective dose for adults, the agency sees no reason to exclude it from the children's dosage schedule as the minimal effective dose for children over 9 years of age. The agency has no data to show that a minimal effective dose for children over 9 years of age poses a danger of therapeutic failure and subsequent overdose with resultant toxicity, as is the case with younger age groups.

In view of the above discussion, the children's dosage schedule for aspirin, acetaminophen, and sodium salicylate that is based upon the children's dosage unit of 80 mg or 81 mg is as follows:

Age (years)	Number of 80-mg or 81-mg dosage units	Dosage (mg)
Under 2	Consult a doctor	
2 to under 4	2	160 or 162
4 to under 6	3	240 or 243
6 to under 9	4	320 or 324

Age (years)	Number of 80-mg or 81-mg dosage units	Dosage (mg) [1]
9 to under 11	4 to 5	320 to 405
11 to under 12	4 to 6	320 to 486

[1] Dose may be repeated every 4 hours while symptoms persist, up to five times a day or as directed by a doctor.

The children's dosage schedule for aspirin, aceaminophen, and sodium salicylate that is based upon the adult dosage unit of 325 mg is as follows:

Age (Years)	Number of 325-mg dosage units	Dosage (mg) [1]
Under 2	Consult a doctor.	
2 to under 4	1/2	162.5
4 to under 6	3/4	243.8
6 to under 9	1	325
9 to under 11	1 to 1¼	325 to 406.3
11 to under 12	1 to 1½	325 to 487.5

[1] Dose may be repeated every 4 hours while symptoms persist, up to five times a day or as directed by a doctor.

In § 343.50(d)(1) in the tentative final monograph, the agency is converting the dosage information in the schedules above to directions that provide concise instructions for the consumer. The agency proposes that adult dosage unit strengths exceeding 325 mg, particularly in solid dosage forms, are not suitable for use in children, because of the difficulty in dividing such dosage units to obtain an accurate children's dose.

Children's dosage units comparable to the 80-mg and 81-mg units discussed above are being proposed for carbaspirin calcium, choline salicylate, and magnesium salicylate in § 343.50(d)(4), (5), and (6) in this tentative final monograph.

Reference

(1) "United States Pharmacopeia XIX," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 39, 1975.

59. Two comments objected to the Panel's recommendation that dosage schedules for children should be based on age, asserting that they should be based on weight instead. The comments argued that dosages based on age are inaccurate because any group of children of the same age will vary in size and weight, and that the dosage schedules of virtually all other drugs are based on weight rather than age. A comment also stated that the recommended children's dosages, with relatively slight differences between adjacent age groups, are unduly complex and unwarranted.

The Panel, in reaching its recommendation on a children's dosage schedule, considered extensive data and information on pediatric dosage regimens, including toxicity potential, dosage calculation based on weight versus body surface area, and adequacy of product labeling (42 FR 35366). The agency agrees with the Panel that a children's dosage schedule based on age is acceptable because it correlates closely with dosages calculated on the basis of surface area, and because the average consumer will more readily understand such a schedule, as people usually know the child's age but do not always know the child's weight.

In addition, the agency has published a notice of intent requesting comments concerning pediatric dosing information for all OTC drug products. (See the Federal Register of June 20, 1988; 53 FR 23180.) This notice invites public comment on how pediatric dosing information can best be presented in OTC drug product labeling. This notice mentions that comments made in response to several OTC cough-cold tentative final monographs requested that pediatric dosages for cough-cold drug products provide a greater subdivision of age ranges that more closely approximate weight-based dosages and that are similar to the age ranges recommended by the Internal Analgesic Panel for OTC internal analgesic-antipyretic drug products for children. The notice also discusses requests that the use of weight ranges be allowed, on an optional basis, in OTC drug pediatric labeling in addition to age range labeling (53 FR 23183). The agency has not proposed any regulatory changes in this notice, but will consider all aspects for pediatric dosing information, including the use of weight ranges, for all OTC drug products in a future Federal Register publication.

60. One comment suggested that children aged 2 to 3 years be excluded from the children's dosage schedule for OTC aspirin drug products because they cannot communicate symptoms of disease, and these symptoms are often difficult for parents to recognize. The comment suggested that the directions for children aged 2 to 3 years should be "as directed by a physician" because illness can develop rapidly within this age group.

The agency agrees with the Panel's recommendation that the minimum age for OTC use of analgesic-antipyretic drugs is 2 years. Aspirin is used in children 2 to 3 years of age primarily to reduce fever and relieve the aches and pains that often accompany it—symptoms that children can communicate to parents or that parents can readily recognize. Based upon pharmacokinetic considerations and clinical data, the Panel recommended a safe and effective dosage schedule that could be followed by parents in treating children over 2 years of age. The agency concurs with this dosage schedule. However, the agency emphasizes that if the fever persists, the underlying cause of the fever should be determined and treated by a physician. The warnings in § 343.50(c)(2)(i) and (3) for analgesic-antipyretic drug products, limiting use for fever in children to 3 days unless directed by a doctor and advising physician consultation for persistent or worsening fever or new symptoms, are guides to parents in the safe and effective use of these products in children, as are the directions for use in § 343.50(d).

61. One comment suggested that the children's dosage schedule be more clearly displayed and that duplicate words and phrases be eliminated. Another comment stated that the dosage schedule recommended by the Panel is confusing and complex because dosage regimens are provided for ingredients as analgesics and as antipyretics, with doses listed in exact figures (such as 7.38 gr and 59.63 gr) rather than rounded figures.

The children's dosage schedule is intended to indicate clearly to drug manufacturers the specific dose of particular ingredients for specific age groups. However, these dosage schedules are not intended to appear on the label in the format they appear in the monograph. Rather, the label directions should use dosage form units (tablets, capsules, measure of liquid) and should specify, based on the monograph, the quantity of drug in each children's dosage unit and the dosage intervals.

In addition, information contained in the monograph labeling directions may be condensed on the label to provide concise dosage instructions for the consumer. Duplicated words and phrases may be eliminated. The children's dosage schedules for 80-mg, 81-mg, and 325-mg dosage units have been converted to directions that provide concise instructions for the consumer. (See § 343.50(d)(1).)

62. One comment requested that the agency allow a dosage schedule of 15 gr (975 mg) aspirin every 4 hours up to four doses (4 g) per day. The comment provided data to support its view that such a dosage regimen does not present a serious threat of toxicity (Ref. 1). The comment also maintained that this dosage schedule, rather than a 6-hour schedule, would offer consumers the convenience of undisrupted sleep.

A reply comment stated that the dosage schedule recommended by the

Panel should be followed and that no deviations from this schedule should be allowed. The reply comment expressed concern that the 975-mg dose of aspirin might be used beyond the daily maximum of four doses and present a toxicity problem.

The agency disagrees with the comment's request for an aspirin dosage regimen of 15 gr (975 mg) aspirin every 4 hours, not to exceed four doses per day. The agency concurs with the Panel's statement that this dosage regimen would not provide any significant improvement in analgesic or antipyretic effectiveness (42 FR 35361). Furthermore, although the total daily dosage of this regimen does not exceed the maximum aspirin daily dosage of 4 g (60 gr), the agency is concerned that a four-hour dosage interval for a 975 mg dose may result in consumers ignoring the daily maximum limit of four doses with continued use possibly leading to salicylate toxicity. (See also comment 63 below.)

Reference

(1) Comment No. C00060, Docket No. 77N-0094, Dockets Management Branch.

63. Two comments objected to the Panel's recommendation that following an initial dose of 1,000 mg acetaminophen (two dosage units of 500 mg each), subsequent doses should be restricted to 500 mg every 3 hours or 1,000 mg every 6 hours. Stating that this recommendation was based upon the dosage recommended for aspirin, the comments contended that, given the linear pharmacokinetics of acetaminophen, it is irrational to base acetaminophen's dosage and frequency of administration on the nonlinear pharmacokinetics of aspirin. One comment urged that the dosage for acetaminophen be 1,000 mg every 4 to 6 hours, not to exceed 4 g in 24 hours.

The agency is not adopting the comment's recommendation of an acetaminophen dosage regimen of 1,000 mg every 4 hours for the same reason it is not adopting the regimen of 975 mg aspirin every 4 hours. (See comment 62 above.)

The agency believes at this time that it is reasonable for acetaminophen and aspirin to have the same dosage and frequency of administration because, based upon the data submitted to the Panel, the safe and effective OTC dosage ranges for acetaminophen and aspirin are the same—325 mg to 650 mg every 4 hours, not to exceed 4 g in 24 hours. Also, aspirin and acetaminophen are indicated for the same OTC uses, have been extensively promoted as comparable OTC analgesics (with different side effects), and are widely and interchangeably used by consumers.

The agency concurs with the Panel's recommended acetaminophen dosage regimens of 500 mg every 3 hours and 1,000 mg every 6 hours because these dosages are in accord with the safe and effective dosage range for acetaminophen, i.e., 325 mg to 650 mg every four hours (not to exceed 4 g in 24 hours). Based on computer simulations (Ref. 1), pharmacokinetic parameters obtained from the literature (Refs. 2 through 5), and bioavailability data comparing a 650-mg dose with a 1,000-mg dose of acetaminophen (Ref. 6), the agency has determined that a 1,000-mg dose of acetaminophen every 6 hours yields a pharmacokinetic profile equivalent to that of a 650-mg dose of acetaminophen every 4 hours. A 500-mg dose of acetaminophen every 3 hours yields a blood level profile that also is similar to that of a 650-mg dose of acetaminophen every 4 hours. Therefore, the agency is proposing alternative dosage regimens for acetaminophen of 500 mg every 3 hours and 1,000 mg every 6 hours as part of the dosage schedule in § 343.50(d)(2) of the tentative final monograph. As discussed in comment 53 above, the agency is proposing the following dosages for acetaminophen, aspirin, and sodium salicylate: 325 to 650 mg every 4 hours, 325 to 500 mg every 3 hours, or 650 to 1,000 mg every 6 hours.

References

(1) OTC Volume 03BTFM.

(2) Albert, K.S., A.J. Sedman, and J.G. Wagner, "Pharmacokinetics of Orally Administered Acetaminophen in Man," *Journal of Pharmacokinetics and Biopharmaceutics*, 2:381–393, 1974.

(3) Cummings A.J., B.K. Martin, and G.S. Park, "Kinetic Considerations Relating to the Accrual and Elimination of Drug Metabolites," *British Journal of Pharmacology and Chemotherapy*, 29:136–149, 1967.

(4) Slattery, J.T., and G. Levy, "Acetaminophen Kinetics in Acutely Poisoned Patients," *Clinical Pharmacology and Therapeutics*, 25:184–195, 1979.

(5) Prescott, L. F., and N. Wright, "The Effects of Hepatic and Renal Damage on Paracetamol Metabolism and Excretion Following Overdosage: A Pharmacokinetic Study," *British Journal of Pharmacology*, 49:602–613, 1973.

(6) Research Division, McNeil Laboratories, Inc., "Acetaminophen Plasma Level Profile Following Tylenol Acetaminophen Extra Strength Capsules and APAP/R.S. Acetaminophen Tablets, Metabolic Study No. 54," Biochemical Research Report No. 199 (780306), unpublished report, included in OTC Volume 03BTFM.

64. One comment requested that the Panel's recommended monograph be revised to state that 377 mg magnesium salicylate is equivalent to 325 mg sodium salicylate rather than the 325-mg quantity of magnesium salicylate specified by the Panel (42 FR 35420). The comment explained that commercial sodium salicylate is substantially anhydrous (Refs. 1 and 2), but that magnesium salicylate is commercially available as the tetrahydrate, which contains the equivalent of about 74.5 percent salicylic acid. Assuming that the salicylic acid content is the active moiety of analgesic salicylates and because sodium salicylate contains 86.3 percent salicylic acid, the comment calculated that about 1.16 times more magnesium salicylate tetrahydrate, or 377 mg (325 mg x 1.16), is needed to be equivalent to 325 mg sodium salicylate.

The comment also pointed out that the Panel's recommended monograph does not state the molecular composition of magnesium salicylate and requested that it be clarified to state that 377 mg magnesium salicylate tetrahydrate is equivalent to 325 mg sodium salicylate. The comment concluded that, as stated in the Panel's monograph, one could assume that the difference in the salicylic acid content between 325-mg doses of magnesium salicylate and sodium salicylate could affect the therapeutic response, especially in a multidose regimen.

The agency agrees that 377 mg magnesium salicylate tetrahydrate is equivalent to 325 mg sodium salicylate. The Panel's recommendation of 325 to 650 mg magnesium salicylate every 4 hours for analgesic effect was based on data submitted on a product containing 325 mg of the tetrahydrate form of magnesium salicylate (Ref. 3). However, for adult dosage schedules for aspirin, acetaminophen, and sodium salicylate, the Panel recommended a minimum effective dosage of 325 mg for each of these ingredients (42 FR 35358), with which the agency concurs. Based upon a minimum effective dosage of 325 mg sodium salicylate, the minimum effective dosage of magnesium salicylate tetrahydrate that would contain an equivalent amount of salicylic acid is 377 mg. Therefore, the maximum dosage for magnesium salicylate should be 754 mg instead of 650 mg, and the dosages for magnesium salicylate are being revised accordingly in this tentative final monograph, which now also specifies that the dosages are based on the tetrahydrate form of magnesium salicylate (§ 343.50(d)(6)).

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1120, 1976.

(2) "National Formulary XIV," American Pharmaceutical Association, Washington, p. 656, 1975.

(3) OTC Volume 030042.

F. Comments on Combination Drug Products and Inactive Ingredients

65. One comment objected to the Panel's recommendation in § 343.20 for combining 325 mg each of aspirin and acetaminophen in a single dosage unit for OTC use. The comment contended that because of the complex pharmacokinetics of aspirin, any combination of aspirin and acetaminophen should be subject to the requirements of a new drug application (NDA). Referring to a study by Cotty et al. (Ref. 1), the comment stated that using acetaminophen and aspirin together results in higher blood levels of aspirin than when the same quantity of aspirin is administered alone.

Other comments supported the recommended provision for combining aspirin and acetaminophen. These comments stated that such a combination should not be precluded and may be useful by sparing the side effects of each ingredient. One comment also referred to the srudy by Cotty et al. (Ref. 1) and argued that concomitant use of aspirin and acetaminophen resulted in higher blood levels of unhydrolyzed aspirin, and not total salicylate, and that except for "very specific side effects" this should not be associated with an increase in overall toxicity.

The study by Cotty et al. (Ref. 1) indicates that acetaminophen administered with aspirin appeared to increase blood concentrations of unhydrolyzed aspirin. These investigators expected no increase in toxicity because the toxicities of salicylic acid and aspirin are similar. They concluded that the increase in aspirin blood concentration and duration would be expected "to produce a net increase in pharmacologic activity over the sum of the activities of the individual drugs administered alone" because aspirin is a more potent analgesic than salicylic acid. However, this conclusion is not supported by the results of a study by Wallenstein (Ref. 2). This study demonstrated that a subtherapeutic combination of 210 mg aspirin and 150 mg acetaminophen (a 360-mg total) was essentially equivalent in analgesic effect to 360 mg of either ingredient alone and that 420 mg aspirin combined with 300 mg acetaminophen was essentially equivalent in analgesic effect to 720 mg of either ingredient alone.

After evaluating the studies discussed above, the agency concludes that the combination containing 325 mg each of aspirin and acetaminophen does not increase the overall toxicity of either ingredient in adults. (For a discussion of the use of OTC internal analgesic-antipyretic combination drug products in children, see comment 66 below.) The data provided do not support the comment's contention that because of the "complex pharmacokinetics of aspirin," combinations of aspirin and acetaminophen should be subject to the requirements of an NDA. Therefore the Panel's provision for a combination containing a 325-mg minimal effective dose each of aspirin and acetaminophen is being proposed in this monograph. However, unlike the Panel's recommendation in § 343.20(a) (1) and (2), the tentative final monograph does not require that 325 mg of each ingredient be contained in a single dosage unit. (See comment 72 below.)

References

(1) Cotty, V.O.F., et al., "Augmentation of Human Blood Acetylsalicylate Concentrations by the Simultaneous Administration of Acetaminophen with Aspirin," *Toxicology and Applied Pharmacology*, 41:7–13, 1977.

(2) Wallenstein, S.L., "Analgesic Studies of Aspirin in Cancer Patients," *Proceedings of the Aspirin Symposium*, The Aspirin Foundation, London, pp. 5–10, 1975.

66. Two comments urged that dosage schedules for children under 12 years of age be provided in § 343.20 (b) and (c) for the permitted OTC internal analgesic combination drug products recommended by the Panel in § 343.20(a). The comments asserted that the Panel's recommendations unnecessarily restrict product use by specifying only adult dosages for analgesic or antipyretic combinations and that this position contradicts other sections of the recommended monograph in which children's dosages are specified by age groups for single ingredient products, e.g., § 343.10(a) (1)(i) and (2).

The agency is concerned about the risks that may be associated with the use of analgesic-antipyretic combinations in children. For example, Bickers and Roberts observed a case of intoxication in a 5½-year-old child after a combined regimen of 300 mg aspirin and 300 mg acetaminophen, alternating every 2 hours for fever (Ref. 1). (Each drug was given individually every 4 hours.) The authors pointed out that, although many of the findings in the patient were characteristic of "simple" poisoning with either drug alone, this particular case presented difficulties in diagnosis, prognosis, and treatment strategy.

Although this patient's medication history involved more than the combined regimen of aspirin and acetaminophen, the agency shares the authors' concerns about intoxication from a combined regimen of aspirin and acetaminophen in children and notes their contention that the basis for prescribing such a regimen is wholly inadequate. In addition, the only combinations provided for in this tentative final monograph contain acetaminophen with aspirin or other salicylates. Because the agency is not aware of any data supporting the safe use of such analgesic combinations in children or any such combinations marketed for children, combinations of analgesic-antipyretic ingredients in § 343.20(a) are not being proposed for use by children under 12 years of age in the tentative final monograph.

Internal analgesic combinations containing nonanalgesic ingredients in § 343.20(b) in this tentative final monograph and the pediatric (or children's) dosages of such products will have to comply with the children's analgesic dosages included in the final monograph for OTC internal analgesic drug products. (See comment 67 below for further discussion of combination drug products containing analgesic and cough/cold ingredients.)

Reference

(1) Bickers, R.G., and R.J. Roberts, "Combined Aspirin/Acetaminophen Intoxication," *Journal of Pediatrics*, 94:1001–1003, 1979.

67. One comment objected to the Panel's recommendation that combination products be labeled to reflect all of the approved pharmacological activities of the active ingredients (42 FR 35370). The comment maintained that such labeling on a combination product containing active ingredients intended to relieve different symptoms, such as those of the common cold, would be confusing and misleading to consumers because they might think the product should be used only when all the symptoms are present. The comment stated that a combination product containing an analgesic-antipyretic ingredient should not be avoided because a single symptom of only pain or fever is present rather than both symptoms. The comment recommended that the phrase in § 343.20(d)(1), (2), (3), and (4) that states "* * * the product is labeled for the concurrent symptoms involved, * * *"

be replaced by the following statement: "The product must be labeled to reflect all of the proven pharmacological activities of the active ingredient(s) consistent with the recommended use of the product."

The agency agrees that a combination product containing an analgesic-antipyretic ingredient should not be avoided just because an individual has a single symptom of pain or fever, rather than both symptoms. As discussed in comment 16 above, the indications statement for analgesic-antipyretic ingredients in § 343.50(a)(1) is being revised to allow manufacturers flexibility in stating the uses for these ingredients.

The agency recognizes that combination products may be intended for use by a specific target population, such as consumers who are suffering from the common cold with minor pain or fever. The agency believes that the labeling for such combinations should reflect the principal intended use(s) of the product (e.g., pain reliever-fever reducer and nasal decongestant). Such labeling should be consistent with the approved indications for the active ingredients, but would not be required to contain all of the indications.

The agency believes that labeling specific to analgesic/cough-cold combinations need only appear in one monograph, which should be the one most pertinent to the intended target population of the combination product. Therefore, the agency has determined that the labeling for analgesic/cough-cold combination products should be included in the combinations segment of the cough-cold tentative final monograph, which was published in the Federal Register of August 12, 1988 (53 FR 30522). Accordingly, the Panel's specific recommendations in § 343.20(d)(1), (2), (3), and (4) of its monograph are not being addressed in this tentative final monograph. However, the agency has included a statement in the combinations section (§ 343.60(b)) of this tentative final monograph stating basically what the comment requested, i.e., that the labeling of the product states the indications for each ingredient in the combination, as established in the indications section of the applicable OTC drug monographs. Further, the agency has stated in § 343.60(b)(3) that for analgesic-antipyretic/cough-cold combinations, the indications stated in the cough-cold monograph should be used.

68. One comment objected to the word "essential" in the following statement in the Panel's report (42 FR 35370):

" * * * that marketed products contain only those ingredients essential to the product." The comment argued that the word "essential" is too restrictive for OTC drug products. The comment maintained that some consumers might consider inactive ingredients nonessential, but other consumers consider these ingredients, such as a color or a flavor, essential to their acceptance of the product and their compliance with the directions for use. The comment recommended that excipients that contribute to patient acceptance of a product be permitted, along with those excipients necessary to prepare the final dosage form and provide stability and availability.

The phrase regarding essential ingredients was actually part of a recommendation by the Cough-Cold Panel, with which the Internal Analgesic Panel concurred (43 FR 35370). The Internal Analgesic Panel stated that it was aware of the inclusion of inactive ingredients in marketed drug products as "fillers, coatings, colorants, vehicles, aromatics, binders, sweeteners, flavoring agents, etc." and that "Such inactive ingredients are acceptable for marketing purposes provided they are pharmacologically inert and do not adversely affect the bioavailability of the active ingredients * * *." (See 43 FR 35370.)

The OTC drug review is an active, not an inactive, ingredient review. The OTC panels occasionally made recommendations with respect to inactive ingredients; however, these recommendations were made for public awareness and comment and were not intended to be included in the OTC drug monographs. Although not included in OTC drug monographs, inactive ingredients must meet the requirements of § 330.1(e) that they be ingredients that are safe and do not interfere with the effectiveness of the product or with tests to be performed on the product.

69. One comment stated that §§ 343.10(a)(2) and 343.12(a)(2) of the Panel's recommended monograph are inconsistent with § 341.20(e) of the Cough-Cold Panel's recommended monograph. The comment requested that § 341.20(e) be revised to allow children's dosages for combination products containing phenylpropanolamine, a nasal decongestant, and analgesic-antipyretic active ingredients. The comment suggested a revision in the phenylpropanolamine dosage to be consistent with the children's dosage of analgesic-antipyretic active ingredients.

This comment was submitted to both the OTC internal analgesic and the OTC cough-cold rulemakings. Adjustment of the dosage of phenylpropanolamine will be addressed in a future issue of the Federal Register in an amendment to the nasal decongestant portion of the cough-cold tentative final monograph. The comment was also addressed in the cough-cold combination drug products tentative final monograph (see comment 60 at 53 FR 30550).

70. Citing sections 201(p), 502(f), and 505(b) of the act (21 U.S.C. 321(p), 352(f), and 355(b)), one comment contended that the safety and effectiveness of a combination drug product as a whole should be the criteria by which it is judged, rather than the safety and effectiveness of its individual active ingredients. The comment stated that clinical testing of the contribution of each ingredient in a combination drug product would cause unnecessary expense for the manufacturer of the product. The comment suggested an alternative combination policy that would allow any number of ingredients to be included in a combination drug product in any quantity up to their maximum OTC dosage level as single ingredients, provided that the ingredients would not add a significant risk of harm from use or neutralize the effectiveness of other ingredients in the product. Based upon this suggestion, the comment requested Category I status for a combination drug product containing aspirin, acetaminophen, salicylamide, and caffeine, noting that the Panel classified as Category III both salicylamide and caffeine as analgesic adjuvants (42 FR 35483 and 35486).

The OTC drug review regulation for OTC combination drug products in § 330.10(a)(4)(iv) (21 CFR 330.10(a)(4)(iv)), which implements provisions of the act, states that:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The requirements for OTC combination drug products have been further delineated in the agency's "General Guidelines for OTC Drug Combination Products" (Ref. 1). Item 4 under these guidelines states:

> An ingredient claimed to be a pharmacological adjuvant (i.e., to enhance or otherwise alter the effect of another active ingredient) will be considered an active ingredient. Such an ingredient may be included in addition to one or more principal

active ingredients only if it meets the combination policy in all respects.

Item 5 under the OTC combination drug product guidelines states:

In some cases an ingredient may be appropriate for use only in a specific combination or data may be available only to support the use of the ingredient in combination but not as a single ingredient. In such cases the ingredient will be placed in Category I for use only in permissible combinations and not as a single ingredient.

Both salicylamide and caffeine are being classified as Category III ingredients in this tentative final monograph (see comments 91 and 93 below). However, if data were submitted to show that either or both of these ingredients contributed to the claimed effect of the combination, the ingredient(s) could be included in the combination in accordance with the guidelines.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D-0322, Dockets Management Branch.

71. One comment argued that although the Panel placed aspirin, acetaminophen, and several other analgesics in Category I, none of the combinations that are commonly used for headache has been classified as Category I. The comment urged that such combinations be kept on the OTC market because they have been commonly used and have met individual needs where single-ingredient products did not. (The comment did not name any specific products.)

Because the comment did not name any specific combination drug products or provide data on them, the agency is unable to consider the comment's arguments at this time. As previously mentioned, the regulations for OTC combination drug products have been supplemented by "General Guidelines for OTC Drug Combination Products" (see comment 70 above). The status of OTC analgesic combinations will be determined according to the regulations and these supplementary guidelines.

72. Several comments disagreed with the Panel's recommendations in §§ 343.20 (a), (b), and (c) that would permit combinations of two Category I internal analgesic-antipyretic ingredients only at the dosage limits specified and in a single large dosage unit. One comment contended that each analgesic ingredient in a combination should be permitted in lower than effective doses when such a combination can achieve a therapeutic effect similar to the higher quantity of a single ingredient. Other comments objected to combining the ingredients into a single large dosage unit. These comments requested that pharmaceutical manufacturers be allowed to divide the dosage between two smaller dosage units, with labeling directing consumers to take two dosage units per dose. The comments contended that one large dosage unit would be difficult to swallow and may lead to overdosage by consumers who are used to taking two tablets per dose. The comments also argued that such a requirement would burden pharmaceutical manufacturers and consumers with increased costs associated with retooling machinery used to make the larger dosage unit, redesigning packaging, etc.

The Panel recommended that only combinations containing the minimal effective adult dose of each analgesic-antipyretic ingredient be permitted. In the absence of data demonstrating that amounts less than the minimum effective dose contribute to effectiveness, the agency concurs with this recommendation as it applies to dosage level. However, the agency does not believe it is necessary to place specific restrictions on the amounts of active ingredients to be contained in a single dosage unit, provided the product's recommended dosage meets monograph conditions. The agency agrees with the comment that pharmaceutical manufacturers should be allowed to divide the dose of a combination product into more than one dosage unit with compensating directions for use. For example, the dosage for a tablet containing 162.5 mg of aspirin and 162.5 mg of acetaminophen would be two tablets per dose, thus meeting the minimum effective dosage requirements for each ingredient. Thus, the Panel's recommendation for a single dosage unit to contain the minimal effective dosage of each analgesic ingredient in § 343.20(a) is not being included in the tentative final monograph.

In addition, the agency has expanded the allowable combinations recommended by the Panel by proposing in § 343.20(a) to permit a range of acceptable amounts of active ingredients beyond the minimum effective dose to be contained in combination products. Based on the quantities of active ingredients in the products, the dosage schedules for analgesic-antipyretic combinations must comply with the dosages provided in § 343.60(d)(1) (i) or (ii) under the directions for use. (See also comment 65 above.)

With regard to the combinations of analgesic-antipyretic ingredients, the Panel based its recommendations on the review of single Category I ingredients as well as on data submitted on combination products. After the Panel's report was published in July 1977, the agency published "General Guideline for for OTC Drug Combination Products" (Ref. 1). The guidelines include a description of the criteria for the combination of Category I active ingredients from the same therapeutic category having the same or different mechanisms of action.

The agency believes that the Panel's recommendations for Category I classification of combining acetaminophen with aspirin or other Category I salicylates is in accordance with Item 2 of the OTC combination drug product guidelines, which states:

Category I active ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the OTC combination policy in all respects and the combination is on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. Such combinations may utilize each active ingredient in full therapeutic dosage or sub-therapeutic dosage, as appropriate.

Therefore, the agency proposes to include combinations of acetaminophen with aspirin or other Category I salicylates in this monograph under § 343.20(a).

With regard to the Panel's recommendations of combining aspirin and other Category I salicylates with each other, the agency finds no data referred to in the Panel's report to support such combinations and further finds that such combinations are not in accordance with the guidelines as described in Item 3, which states:

Category I active ingredient from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. They may be combined in selected circumstances to treat the same symptoms or conditions if the combination meets the OTC combination policy in all respects, the combination offers some advantage over the active ingredients used alone, and the combination is, on the benefit-risk basis, equal to or better than each of the active ingredients used alone at this therapeutic dose.

In addition, following publication of the Panel's report the agency has received no data or information on such combinations, nor is aware of any such OTC drug products on the market.

Therefore, the agency is proposing not to include analgesic-antipyretic combinations that contain only salicylates in this monograph. The agency invites comment on this position.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D-0322, Dockets Management Branch.

73. One comment noted that the Panel's recommendation in § 343.20 does not provide for combinations of analgesic-antipyretic ingredients with both nasal decongestants and antihistamines, although provision was made for combination drug products containing an analgesic-antipyretic ingredient with either a nasal decongestant or an antihistamine. The comment asserted that information regarding a combination drug product containing analgesic-antipyretic ingredients, a nasal decongestant, and an antihistamine was submitted to the Panel and that such a product is consistent with the Category I combination drug products allowed in § 341.40(c) of the advance notice of proposed rulemaking on OTC cough-cold drug products. The comment requested that such a combination be incorporated into § 343.20 of the recommended OTC internal analgesic monograph.

The agency has determined that the categorization of combinations containing antihistamine and nasal decongestant ingredients properly falls within the scope of the OTC cough-cold drug product rulemaking. As mentioned in comment 67 above, the agency addressed combination drug products containing antihistamine, nasal decongestant, and analgesic-antipyretic active ingredients in the tentative final monograph for cough-cold combination drug products. (See comment 47 at 53 FR 30540.)

74. One comment opposed the 3-hour to 6-hour dosage interval recommended by the Panel for acetaminophen in § 343.10(b)(3) because it is incompatible with the 4-hour dosage interval for nasal decongestants and precludes the manufacture of a combination drug product containing acetaminophen and a nasal decongestant. The comment also argued that a 3-hour or a 6-hour dosage interval would be "foreign" to the habits of consumers, physicians, and pharmacists and would undesirably affect patient compliance.

The tentative final monograph on OTC internal analgesic drug products contains dosage schedules of acetaminophen based on 4-hour as well as 3-hour and 6-hour intervals. Thus, dosage schedules for this ingredient that are compatible with those specified for Category I oral nasal decongestants can be achieved. The agency does not believe that a dosage interval of every 6 hours would be foreign to the habits of consumers or would have an undesirable effect on patient compliance because many drugs are taken at 6-hour intervals.

G. Comments on Definitions.

75. One comment proposed that the following definition be included in § 343.3: "*Powdered aspirin analgesic.* A powdered form of aspirin packaged in individual unit doses."

The agency notes that the definitions recommended by the Panel in § 343.3 are general in nature and applicable to all dosage forms, and thus there would have been no reason for the Panel to include a definition of powdered aspirin. The agency sees no need to include this definition, and, in order to conform with format and style of recently published monographs, the definition section is being revised in the tentative final monograph to contain only one definition: analgesic-antipyretic drug.

76. One comment requested that the definition of highly buffered aspirin for solution in recommended § 343.3(k) be amended from "* * * contains at least 20 mEq of acid neutralizing capacity per 325 mg of aspirin and results in a pH of 3.5 or greater at the level of the initial 10 minute period as measured by the method established in § 331.25 of this chapter * * *." to "* * * provides at least 15 mEq of acid neutralizing capacity as measured by the method established in § 331.26 of this chapter * * *." The comment also requested that recommended § 343.20(d)(6), which refers to the combination of aspirin with an antacid, be revised accordingly. The comment presented data to show that a currently marketed highly buffered aspirin for solution product has less than 20 mEq of acid-neutralizing capacity per 325 mg aspirin and cited a submission to the Panel showing that the acid-neutralizing capacity of this product is 16.5 mEq when tested by the method in § 331.26 (Ref. 1).

After reviewing the submission to the Panel and testing the marketed product mentioned by the comment, the agency agrees that the product has less than 20 mEq of acid-neutralizing capacity per 325 mg aspirin. The agency points out that an average of 5 mEq is the minimal acid-neutralizing capacity required for an antacid to combine with the residual gastric acid and to maintain an elevated pH for 15 minutes in a normal subject. (See the advance notice of proposed rulemaking on OTC antacid drug products published in the Federal Register of April 5, 1973 (38 FR 8717).) Thus, a finished product must have an acid-neutralizing capacity of at least 5 mEq (§ 331.10) (21 CFR 331.10) to be labeled as an antacid. Highly buffered aspirin for solution exceeds this requirement. However, this is only one example of currently marketed drug products that contain aspirin with antacid ingredients (identified in § 331.11) in sufficient concentration to provide at least 5 mEq of acid-neutralizing capacity, thereby providing antacid activity in addition to analgesic activity.

The agency is not including the Panel's definition in § 343.3(k) because this information is contained in § 343.20(b)(3) of this tentative final monograph and is being revised to include all products containing aspirin with antacids that are generally recognized as safe and effective (i.e., those products providing at least 5 mEq of acid-neutralizing capacity) instead of highly buffered aspirin for solution only: "Aspirin identified in § 343.10(b)(1) may be combined with any antacid ingredient identified in § 331.11 or any combination of antacids permitted in accordance with § 331.10(a) provided that the finished product meets the requirements of § 331.10, is marketed in a form intended for ingestion as a solution, and bears labeling indications in accordance with § 343.60(b)(4)." Elsewhere in this issue of the Federal Register the agency is proposing to amend § 331.15 of the final monograph on OTC antacid drug products so that the combinations of antacids with nonantacid active ingredients listed therein will be consistent with the combinations being proposed in this tentative final monograph. (See also comment 47 above.)

The comment gave no reason for excluding the antacid test in § 331.25. This test should precede the test to determine the acid-neutralizing capacity of a product as specified in § 331.26. Both tests are required under § 331.10 for antacid products and have been retained here for aspirin with antacid products.

Reference

(1) OTC Volume 030104.

77. One comment recommended deleting the pH requirement from the definition of buffered aspirin in § 343.3(j), i.e., "* * * results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of this chapter * * *." The comment argued that the requirement is unnecessarily

restrictive because it is not crucial to the definition. Another comment stated it is unclear whether the 1.9 mEq in the definition is meant to be measured or calculated, and whether it refers to 1.9 mEq of antacid ingredients per 325 mg aspirin or to 1.9 mEq of acid-neutralizing capacity above what is needed to neutralize the aspirin. This comment also stated that the pH requirement is an antacid requirement and is inappropriate for a buffered aspirin product because buffered aspirin products currently on the market theoretically do not contain sufficient antacid to raise the pH of 10 mL of 0.5 Normal hydrochloric acid to 3.5.

The comment suggested a revised definition of buffered aspirin to replace the one recommended in § 343.3(j) and gave details for a testing procedure to replace the one in the Panel's report at 42 FR 35488, which is the same as the procedure specified in § 331.26. The comment stated that the test it suggested would eliminate poorly formulated or unstable products that contain an ineffective or partially reactive antacid.

The agency is proposing only one definition in the tentative final monograph: Analgesic-antipyretic drug. Therefore the comment's request will not be discussed in the context of the monograph definitions. However, § 343.10(b)(2) of this tentative final monograph contains the same information as the Panel's definition and specifies for buffered aspirin that "* * * the finished product contains at least 1.9 millequivalents of acid-neutralizing capacity per 325 mg aspirin * * *." Because the finished product is to be tested, there must be sufficient antacid ingredients added to the product so that the finished product provides the specified acid-neutralizing capacity.

As to whether the acid-neutralizing capacity should be measured or calculated, it is apparent the Panel intended the acid-neutralizing capacity to be measured, i.e., experimentally determined, because it specified a test for measuring acid-neutralizing capacity (42 FR 35487 and 35488). Because the method of manufacture or other factors may affect the acid-neutralizing capacity, the theoretical acid-neutralizing capacity of a buffered aspirin product may be different from the experimentally determined capacity. Therefore, the acid-neutralizing capacity is to be experimentally determined (measured).

The requirements for initial pH determination in § 331.25 were devised for antacids, and not all buffered aspirin products contain sufficient quantities of antacid ingredients so that the finished product provides antacid activity. Consequently, buffered aspirin products should not be required to meet all of the standards of the antacid monograph.

To determine the acid-neutralizing capacity of the product, however, the procedure established in § 331.26 must be followed. The agency points out that data submitted to the Panel show that a well-formulated buffered aspirin product provides 1.9 mEq of acid-neutralizing capacity when measured by the method established in § 331.26 (Refs. 1 and 2). After testing buffered aspirin products according to § 331.26 and the comment's method, the agency has determined that the products provide 1.9 mEq of acid-neutralizing capacity when measured by either method. However, the method in § 331.26 is more discriminating. The agency concludes that the comments have not presented sufficient reasons for replacing the established procedure in § 331.26 with the suggested procedure. Accordingly, the agency will retain the procedure in § 331.26.

Based upon the above discussion and for clarity, the Panel's recommended § 343.20(d)(7) (redesignated § 343.10(b)(2) in this tentative final monograph) is being revised as follows: "Buffered aspirin. Aspirin identified in paragraph (b)(1) of this section may be buffered with any antacid ingredient(s) identified in § 331.11 provided that the finished product contains at least 1.9 millequivalents of acid-neutralizing capacity per 325 milligrams of aspirin in accordance with § 331.26."

References

(1) OTC Volume 030136.
(2) OTC Volume 030137.

H. Comments on Effects of Product Formulations on Drug Absorption and Pharmacologic Effectiveness

78. One comment argued that OTC aspirin rectal suppositories should be classified as Category I. The comment maintained that their long history of use and administration to hospital patients who are unable to use oral dosage forms of aspirin have shown that they are effective analgesic-antipyretic drug products and have produced no evidence of rectal irritation.

The comment submitted no data in support of its argument. The Panel noted that the rate of absorption of aspirin from suppositories was slow compared with its absorption from the oral tablet form (42 FR 35377). The Panel noted that because suppositories may have different melting or dissolution rates, therapeutic levels of the active ingredients contained in these dosage forms can be unpredictably high or low, ranging potentially from therapeutically ineffectual results to toxicity. Thus, the Panel placed OTC analgesic rectal suppositories in Category III, concluding that additional bioavailability data and evidence concerning possible rectal irritation are needed for each suppository formulation.

The agency specifically invites comment and submission of data on OTC analgesic rectal suppositories, particularly data on bioavailability and possible rectal irritation, in accordance with the discussion on testing guidelines in part II. paragraph A.2. below and with the feedback procedures published in the Federal Register of September 29, 1981 (46 FR 47740). In the absence of such data at this time, the agency is proposing that OTC analgesic rectal suppositories remain in Category III.

79. One comment stated that a certain timed-release aspirin product with an approved NDA dating from 1965 should not be included in an OTC drug monograph, but should be maintained as a new drug subject to an approved NDA.

The agency agrees with the comment. The particular product in question contains 650 mg aspirin in a timed-release dosage unit, a safe amount for a single dose. However, the recommended dose of the product is two tablets, followed by one to two tablets every 8 hours. A 2-tablet dose (1,300 mg) represents a quantity of active ingredient which, if released from the tablets at one time, is not generally recognized as safe for a single dose in OTC drug products. (The safe maximum single OTC doses for aspirin, as discussed in comment 53 above, are 650 mg every 4 hours or 1,000 mg every 6 hours.)

The agency concludes that this timed-release aspirin product is a new drug under § 200.31 (21 CFR 200.31), and will remain the subject of an approved NDA and not be included in the monograph. Each NDA must contain, among other information, bioavailability data showing that the total dose of the active ingredient is released at a safe rate—that is, not too quickly or too slowly.

I. Comments on Aspirin

80. One comment stated that the amount of aspirin in an OTC internal analgesic drug product should be listed both in grains and milligrams, with grains shown first and milligrams shown parenthetically.

Although manufacturers may voluntarily list quantities of active ingredients in either grains or metric units or both, the agency believes that it would be useful for manufacturers to list ingredients in metric units. The Metric Conversion Act of 1975 (80 Stat. 1007) was enacted to increase voluntarily the use of the metric system of weights and

measures in the United States. In support of this policy, the agency has developed a Compliance Policy Guide (Ref. 1) to establish general and specific guidance for the voluntary use of metric units of quantity on the labeling of FDA-regulated commodities. This guide states that a declaration of quantity of contents in units of weight is expressed in terms of the kilogram, gram, milligram, or microgram. While historically the amount of aspirin in an OTC internal analgesic drug product was listed in apothecary units (grains), based on the Metric Conversion Act of 1975, the agency is encouraging use of milligram units. This approach is consistent with current labeling policy for FDA-regulated commodities.

Reference

(1) "Metric Declaration of Quantity of Contents on Products Labels," reprint of Food and Drug Administration Compliance Policy Guide 7150.17, 1987.

81. One comment stated that the number of tablets in an aspirin product container should be shown on the label.

The agency points out that the declaration of net quantity of contents of an OTC drug package is already provided for in § 201.62(a) (21 CFR 201.62(a)), which states that the "* * * quantity of drugs in tablet, capsule, * * * or other unit form * * * shall be expressed in terms of numerical count * * *." Thus the number of tablets in an aspirin product container is required to be shown on the label.

82. Several comments stated that menstrual blood flow might be increased by the ingestion of aspirin products. One comment stated that many women use products containing aspirin to relieve pain from menstrual cramps and that warnings for these products should indicate that aspirin might increase menstrual blood flow. Another comment stated that aspirin, which appears to be the most commonly used analgesic for menstrual cramps, is not a cause of massive uterine bleeding.

Based on available information, aspirin does not appear to affect normal menstrual blood flow, and there are no data demonstrating that a warning to that effect is necessary. The agency is aware that the Miscellaneous Internal Panel reviewed the use of aspirin for the relief of pain of menstrual cramps and concluded that it is safe for such use. (See the Federal Register of December 7, 1982; 47 FR 55076.) Neither that Panel nor the Internal Analgesic Panel was aware of any evidence that aspirin increases menstrual blood flow.

The direct irritant effects of aspirin upon the gastric mucosa and its effects upon platelet aggregation have been well described in the medical literature, and the possible adverse effects of aspirin upon postoperative bleeding have been well discussed in the literature. It is recognized that doses of aspirin greater than the recommended therapeutic doses may reduce plasma prothrombin by interfering with the role of vitamin K in the production of prothrombin and decreasing platelet aggregation, thus prolonging the coagulation process (42 FR 35384). However, these effects seem to be unrelated to those involved in normal menstrual blood flow.

83. One comment stated that there was no mention in the Panel's recommended monograph of the "unique safety" of the powder dosage form of aspirin compared with other dosage forms. The comment attributed the safety of aspirin powders to their physical form and packaging and presented data to show that there have been only a few accidental ingestions of aspirin powders compared with a large number of accidental ingestions of other forms of aspirin. The comment also pointed out that the Consumer Product Safety Commission (CPSC) exempted aspirin powders from the safety packaging requirements of the Poison Prevention Packaging Act.

No attempt has been made in the tentative final monograph to compare the safety of dosage forms; such a comparison is not the intent of the OTC drug review. The comment's discussion is not related to the Panel's or the agency's conclusions on the absorption and pharmacologic effectiveness of aspirin powders and therefore provides no basis for revising the Panel's recommended monograph.

J. Comment on Acetaminophen

84. One comment disagreed with the Panel's recommendation that the standards for child-resistant safety closures for aspirin products, as set forth in regulations (16 CFR 1700.15 (a), (b), and (c)) established according to the Poison Prevention Packaging Act of 1970, should apply to acetaminophen products as well. This comment requested an exemption for liquid dosage forms of acetaminophen containing less than 1 g of acetaminophen per fluid ounce (oz). Several comments agreed with the Panel and noted that the CPSC proposed in the Federal Register of February 3, 1978 (43 FR 4632) to require child-resistant packaging for acetaminophen preparations containing more than 1 g of acetaminophen in a single package.

CPSC, and not FDA, regulates child-resistant packaging. CPSC issued a final rule in the Federal Register of August 31, 1978 (44 FR 51211), requiring child-resistant packaging for acetaminophen-containing preparations in oral dosage form containing more than 1 g of acetaminophen in a single package. This requirement became effective on February 27, 1980 for acetaminophen products packaged after that date, with the following exceptions: Effervescent acetaminophen preparations and acetaminophen preparations in powder form. The comment requesting an exemption for liquid acetaminophen products with less than 1 g of acetaminophen per fluid oz submitted the same request to CPSC, which, in turn, addressed this issue in its final rule and denied the comment's request for exemption (44 FR 51213). FDA concurs with that decision.

K. Comment on Antipyrine

85. One comment submitted data to upgrade the Category III status of antipyrine to Category I and to eliminate the Panel's recommendation of a single 975-mg dose of antipyrine per 24-hour period. The data consisted of three papers on the metabolism, including the half-life, of antipyrine in animals and humans and addressed the metabolism of antipyrine in blacks (Refs. 1, 2, and 3). The comment stated that "these studies provide assurance that a total daily dosage schedule of 9,000 mg or even 6,000 mg of antipyrine would not result in excessively high blood levels, in spite of the acknowledged extended half-life of the drug."

The agency has reviewed the data cited by the comment and concludes that the data are insufficient to justify Category I status for antipyrine. None of the studies provided any significant data to show that antipyrine is safe after repeated doses or to justify changing the Panel's recommendation of one single 975-mg dose per 24 hours.

The agency agrees with the Panel that more data are needed on the safety of antipyrine and is proposing that this ingredient remain classified as Category III. Because of its long half-life, studies on antipyrine should address the amount of this drug that can be safely given within 24 hours and determine an appropriate dosage interval to prevent a toxic amount of the drug from accumulating in the body. In addition, in order to determine sensitivity to antipyrine, epidemiological studies should be conducted that consider pharmacogenetic factors and include several racial groups.

The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 4).

References

(1) Fraser, H.S., et al., "Factors Affecting Antipyrine Metabolism in West African Villagers," *Clinical Pharmacology and Therapeutics*, 20:369–376, 1976.

(2) Breckenridge, A., and M. Orme, "Clinical Implications of Enzyme Induction," *Annals New York Academy of Sciences*, 179:421–431, 1971.

(3) Vesell, E.S., et al., "Relationship Between Plasma Antipyrine Half-Lives and Hepatic Microsomal Drug Metabolism in Dogs," *Pharmacology*, 10:317–328, 1973.

(4) Letter from W.E. Gilbertson, FDA, to T.E. Watson, T.E. Watson Company, coded LET015 to C00162, Docket No. 77N–0094, Dockets Management Branch.

L. Comment on Quinine

86. One comment stated that despite the side effects (such as ringing in the ears, headache, nausea, and visual disturbances) of quinine in large doses (e.g., 2 g per day), it is effective at much lower doses for nocturnal leg cramps and should remain available OTC for this use. In support of its position, the comment cited "The Pharmacological Basis of Therapeutics," edited by Goodman and Gilman (Ref. 1), which states that the dose of quinine for nocturnal leg cramps is 200 to 300 mg before retiring.

The agency is aware of the nocturnal leg cramp dosage for quinine given in the reference cited by the comment. The use of quinine for nocturnal leg cramps has been addressed by the Miscellaneous Internal Panel in the advance notice of proposed rulemaking entitled, "Quinine for the Treatment of Nocturnal Leg Muscle Cramps for Over-the-Counter Human Use," published in the Federal Register of October 1, 1982 (47 FR 43562). The agency concurred in the Panel's classification of quinine for this use in Category III in the tentative final monograph published in the Federal Register of November 8, 1985 (50 FR 46588).

The agency also agrees with the Internal Analgesic Panel's conclusions that the risk of toxic effects of quinine on the skin (e.g., rashes) and on the gastrointestinal, nervous, and cardiovascular systems outweighs its benefit in relieving pain or fever. In fact, the reference cited by the comment describes the toxicity of quinine and does not include analgesic, antipyretic, or antirheumatic actions as therapeutic uses for this drug (Ref. 1). The agency concurs with the Panel, and is proposing in this tentative final monograph that quinine is Category II when labeled for any OTC antipyretic or internal analgesic use other than the treatment and/or prevention of nocturnal leg muscle cramps.

Reference

(1) "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman, and A. Gilman, MacMillan Publishing Co., Inc., New York, pp. 1062–1065, 1975.

M. Comments on Salsalate

87. One comment requested clarification of the status of salsalate, stating that in the table of active ingredients (42 FR 35350) this ingredient is classified as Category III for analgesic effectiveness, but is classified in the active ingredients section as a Category III analgesic for both safety and effectiveness (42 FR 35443).

The table of active ingredients should have shown Category III status of salsalate as an antirheumatic, antipyretic, and analgesic for both safety and effectiveness. The Panel's classification of salsalate as an analgesic is correct (42 FR 35443), but it should have also been shown as Category III for both safety and effectiveness as an antipyretic and an antirheumatic (42 FR 35452 and 35468).

The Panel's position on the categorization of salsalate can be clarified by reviewing the minutes of the Panel's 28th meeting. These minutes state that "the Panel concluded that salsalate should remain in Category III on the basis of insufficient evidence of safety and effectiveness." Furthermore, the Panel's discussion on the safety of salsalate on pages 35452 and 35468 consists of reference to the safety discussion on page 35443, in which the Panel concluded that there were insufficient data to determine salsalate's safety as an OTC analgesic. Because FDA has received no further data on salsalate to warrant a change if its Category III classification, the agency concurs with the Panel that salsalate is a Category III OTC analgesic, antipyretic, and antirheumatic ingredient.

88. One comment objected to the Panel's recommendation that additional toxicology data, such as teratogenicity studies and effects on various organs, may be needed on salsalate. The comment pointed out that because salsalate is an ester of two molecules of salicylic acid, there is no reason to consider it other than "pharmacologically equivalent to salicylic acid" or to expect metabolites other than those found with sodium salicylate. The comment further argued that, as a salicylate analgesic, salsalate should be considered a "salt or similar variant" of a Category I analgesic and that the crossover bioavailability studies for evaluating analgesic effectiveness (42 FR 35445) should be adequate to establish its effectiveness. Because of the acknowledged differences in absorption rates between salsalate and other salicylates, the comment suggested that a crossover bioavailability study should measure the rates of hydrolysis or dissociation of aspirin, sodium salicylate, and salsalate, and determine the peak plasma levels, the times of peak levels, the fractions of doses absorbed, and the half-life during the recommended dosage period of 10 days for an OTC analgesic.

As the Panel pointed out, data on the pharmacokinetics of salsalate are conflicting and incomplete. The study proposed in the comment should be conducted using analytical procedures that differentiate between parent drug (intact salsalate), salicylic acid, and other metabolites that may be formed. If the study shows that any amount of salsalate is absorbed intact and is present in the blood, then salsalate cannot be considered equivalent to salicylic acid, or a "salt or similar variant" of salicylic acid, and a general toxicological profile will be needed.

89. One comment from a manufacturer inquired whether pharmacokinetic data alone can be used to establish the effectiveness of a Category III antirheumatic active ingredient (salsalate). The firm proposed to use a method that differentiates and quantitates levels of salsalate and salicylic acid in serum. The proposed study would compare the pharmacokinetics of salicylate derived from aspirin with the pharmacokinetics of salicylate derived from salsalate after administration of a single dose each of aspirin and salsalate.

The Panel recommended that effectiveness data on salsalate be required according to its guidelines for antirheumatic drugs, which state that antirheumatic studies should be designed to test the anti-inflammatory activity of an ingredient separate from any other action the ingredient may have and that the studies should be double-blind crossover in design, with aspirin as the standard drug (42 FR 35468). The agency concludes that pharmacokinetic data alone are inadequate to establish the effectiveness status of salsalate as an antirheumatic agent and that controlled clinical studies are needed (Ref. 1).

Reference

(1) Letter from W.E. Gilbertson, FDA, to J. Schaefer, Jr., Fisons Corporation, July 18, 1978, included in OTC Volume 03BTFM.

N. Comment on General Discussion of Antirheumatic Agents

90. One comment stated that, although there is extensive literature on fibrositis, the Panel devoted only one paragraph to this subject in its report and cited no references relating to fibrositis. The comment stated that it appeared that the Panel had deliberately ignored this subject because it would drastically weaken its argument that all inflammatory arthritis is malignant rheumatoid arthritis. The comment pointed out that fibrositis is self-limited and treatable by self-medication, and that much of what is initially diagnosed as probable rheumatoid arthritis is later found to be fibrositis.

The agency notes that the Panel did not suggest that all inflammatory conditions are malignant (progressively degenerating) rheumatoid arthritis. Many of the rheumatic conditions listed in the Panel's report are not malignant conditions. Fibrositis was not discussed in the report because the Panel chose to discuss in detail only the more commonly occurring rheumatic diseases. The agency believes that including a discussion of fibrositis would not have affected the Panel's conclusions on OTC arthritis labeling. Fibrositis is not amenable to self-diagnosis because the presenting symptoms are similar to those of the more serious rheumatic diseases. An indication for fibrositis is being included in the professional labeling section of this tentative final monograph (§ 343.80(a)). The agency's proposals on consumer labeling claims concerning arthritis are discussed in comments 17, 18, and 19 above.

O. Comments on Adjuvants and Corrective Agents

91. Several comments urged that caffeine as an OTC analgesic adjuvant be reclassified from Category III to Category I. The comments cited several studies to support their contention that caffeine is an effective analgesic adjuvant, and also to dispute the Panel's concern that in humans caffeine may interfere with the effectiveness of the antipyretic component in combination drug products containing caffeine and an antipyretic ingredient.

After reviewing the studies cited by the comments, the agency agrees with the Panel that there are insufficient data to reclassify caffeine as an analgesic adjuvant from Category III to Category I or to show that it does nor interfere with the antipyretic activity of analgesic-antipyretic ingredients. Of the studies cited, three presented new data and information (Refs. 1, 2, and 3). In a study by Cass and Frederik (Ref. 1), the investigators concluded that it could not be determined whether the addition of caffeine was a positive or negative factor in assessing analgesic effect. The agency concurs with the authors and concludes that the study fails to demonstrate the contribution of caffeine as an analgesic adjuvant.

Thomas et al. (Ref. 2) studied the metabolism of phenacetin and acetaminophen as single ingredients as well as when each ingredient was combined with aspirin, caffeine, and codeine. This study did not address the effectiveness of caffeine as an analgesic or antipyretic adjuvant and cannot be used as evidence of effectiveness.

Wojcicki et al. (Ref. 3) reported on a double-blind, crossover trial that compared the clinical relief of headache and postoperative pain in patients using three analgesic preparations. The authors concluded that the analgesic effectiveness demonstrated by the preparation containing 500 mg acetaminophen and 50 mg caffeine "suggests that this medication is superior to the preparations that did not contain caffeine. This study is not a true crossover study because only patients who felt that they needed additional analgesics crossed over to the second treatment.

The agency proposes that, in order to establish Category I status for caffeine's effectiveness as an analgesic adjuvant, it must be demonstrated that caffeine makes a positive contribution to the effectiveness of the combination product as an analgesic. If the product also makes antipyretic claims, it must be shown that caffeine does not decrease its antipyretic effectiveness.

The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (address above) (Refs. 4 to 7).[1]

References

(1) Cass, L.J., and W.S. Frederik, "The Augmentation of Analgesic Effect of Aspirin with Phenacetin and Caffeine," *Current Therapeutic Research*, 4:583–588, 1962.

(2) Thomas, B.H., et al., "Effect of Aspirin, Caffeine, and Codeine on the Metabolism of Phenacetin and Acetaminophen," *Clinical Pharmacology and Therapeutics*, 13:906–910, 1972.

(3) Wojcicki, J., et al., "A Double-Blind Comparative Evaluation of Aspirin, Paracetamol and Paracetamol + Caffeine (Finimal) for their Analgesic Effectiveness," *Archivum Immunologiae et Therapiae Experimentalis*, 25:175–179, 1977.

(4) Letter from W.E. Gilbertson, FDA, to T.H. Chambers, Goody's Mfg. Corp., coded LET011 to C00033, Docket No. 77N–0094, Dockets Management Branch.

(5) Letter from W.E. Gilbertson, FDA, to M.A. Bass, the National Association of Pharmaceutical Manufacturers, coded LET012 to C00046, Docket No. 77N–0094, Dockets Management Branch.

(6) Letter from W.E. Gilbertson, FDA, to C.F. Baker, Burroughs Wellcome Co., coded LET013 to C00048, Docket No. 77N–0094, Dockets Management Branch.

(7) Letter from W.E. Gilbertson, FDA, to R.M. Palmes, Bristol-Myers Products, coded LET014 to C00060 and LET010, Docket No. 77N–0094, Dockets Management Branch.

(8) Comment Nos. LET00021, LET00024, LET00029, RFT, SUP00025, SUP00027, SUP00028, SUP00030, and CR00002, Docket No. 77N–0094, Dockets Management Branch.

92. One comment requested that the agency permit the use of caffeine as an adjuvant at dosage levels up to 150 mg per single adult dose, or 75 mg per dosage unit, instead of the Panel's recommended 65 mg per single dose. The comment stated that the Panel's single dose of caffeine (65 mg) in combination with analgesics was inconsistent with the Panel's allowable maximum daily dose of 600 mg caffeine. The comment also pointed out that a 65-mg single dose of caffeine seems inconsistent with the dosage of 100 mg to 200 mg recommended by the Advisory Review Panel on OTC Sedative, Tranquilizer, and Sleep-Aid Drug Products.

The Sleep-Aid Panel recommended dosages for caffeine's use as a stimulant, not as an analgesic-antipyretic adjuvant. The Internal Analgesic Panel, however, reviewed caffeine both as an analgesic-antipyretic active ingredient and as an analgesic-antipyretic adjuvant. Caffeine used alone as an OTC analgesic-antipyretic active ingredient was classified by the Panel as Category II. As an analgesic-antipyretic adjuvant, it was classified by the Panel as Category III.

The agency agrees with the comment that the Panel's report is inconsistent with respect to caffeine dosages. The agency has no objection to a dosage level of 150 mg per single adult dose, which is within the dosage range recommended for restoring alertness or wakefulness by the Sleep-Aid Panel and included by the agency in the final monograph for OTC stimulant drug products which was published in the Federal Register of February 29, 1988 (53 FR 6100). However, because data are still needed to demonstrate effectiveness of caffeine as an adjuvant in combination with analgesic, antipyretic, and antirheumatic ingredients, the agency proposes to

[1] Industry has responded to FDA's concern and provided additional data (Ref. 8) which are currently undergoing review by the agency.

classify it as Category III for this use. (See comment 91 above.)

Reference

(1) OTC Volume 030049.

93. One comment disagreed with the Panel's recommendation that salicylamide be placed in Category III for safety and effectiveness as an OTC analgesic adjuvant. The comment argued that the harmful effects of salicylamide cited by the Panel occur only at doses of 1,000 mg or more and not at the lower doses (650 mg or less) used as an OTC analgesic adjuvant. The comment also stated that the Panel failed to consider 35 submitted references substantiating the safety of salicylamide and that nothing in the Panel's report presents reasons for suspecting that the addition of salicylamide would either detract from the effectiveness of the combination or present any safety risk.

The agency agrees with the Panel that there is insufficient information to determine the safety and effectiveness of salicylamide as an adjuvant or as a single ingredient in internal analgesic drug products. The comment submitted no new data or information to alter this decision.

The Panel did consider the 35 submitted references along with all the other data available on salicylamide in concluding that salicylamide was Category III for safety and effectiveness as an adjuvant and as a single-ingredient internal analgesic (Refs. 1 and 2). Deficiencies in the data on salicylamide available to the Panel are discussed in the Panel's report (42 FR 35439 and 35486).

To justify the inclusion of an adjuvant, such as salicylamide, in a combination drug product, the adjuvant must make a positive contribution to the safety and effectiveness of the combination. (See comment 70 above for further discussion of this subject.) Salicylamide in high doses (600 mg or more) has been shown to inhibit salicylate and acetaminophen metabolism by competing for the glucuronidation pathway (Refs. 2, 3, and 4). This inhibition of the metabolism may result in a prolonged therapeutic effect, which is why salicylamide is claimed to be an adjuvant. Whether salicylamide in low doses (less than 600 mg) in combination with salicylate salts or acetaminophen also delays the metabolism of these analgesics and, if so, to what degree, is not known. Therefore, more data are needed on the pharmacokinetics of salicylamide to establish the safety and effectiveness of this ingredient as an internal analgesic adjuvant in such a formulation.

References

(1) OTC Volume 030069.

(2) OTC Volume 030072.

(3) Levy, G., and J.A. Procknal, "Drug Biotransformation Interactions in Man. I. Mutual Inhibition in Glucuronide Formation of Salicylic Acid and Salicylamide in Man," *Journal of Pharmaceutical Sciences*, 57:1330–1335, 1968.

(4) Levy, G., and H. Yamada, "Drug Biotransformation Interactions in Man. III. Acetaminophen and Salicylamide," *Journal of Pharmaceutical Sciences*, 60:215–221, 1971.

P. Comments on Antacid or Buffering Ingredients

94. One comment questioned which antacid or buffering agents may be used as corrective agents with aspirin. The comment noted that the Panel gave a specific list of ingredients of buffering systems (42 FR 35469), but that the Panel's recommendations in § 343.3 (j) and (k) state that antacid active ingredients identified in § 331.11 may be added to aspirin. The comment urged that any of the antacid active ingredients listed in § 331.11 be permitted in combination with aspirin and that these ingredients not be restricted to those listed at 42 FR 35469.

The agency wishes to clarify that the list of ingredients in the Panel's report (42 FR 35469) was not meant to exclude other ingredients identified in § 331.11 of the antacid final monograph as ingredients of buffering systems for use with aspirin as antacids or correctives. As recommended by the Panel in § 343.20(d) (6) and (7) and § 343.3 (j) and (k) and proposed by the agency in the tentative final monograph, the antacid or buffering agents permitted in buffered aspirin or highly buffered aspirin drug products include all of the ingredients identified in § 331.11 of the final monograph for OTC antacid drug products (21 CFR 331.11).

95. Comments expressed opposing views on whether the agency should reconsider the use of highly buffered aspirin for solution products for the concurrent symptoms of headache and acid indigestion as part of the internal analgesic rulemaking, in view of the agency's final decision to allow such a combination in the final monograph for OTC antacid drug products. The antacid final monograph states in § 331.15(b), "An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution."

The agency stated in the preamble to the final rule for OTC antacid drug products (39 FR 19862) that the Internal Analgesic Panel was reviewing OTC internal analgesics for their safety effectiveness, and appropriate labe and that the analgesic component o antacid-analgesic combination drug product would remain under consideration and would be the subject of a further review and determination by the agency according to the procedures specified in § 330.10. Because a panel may also find it necessary to review the safety, effectiveness, and rationality of combination drug products within which the individual ingredients are contained, it is possible that a particular drug combination may be reviewed by more than one panel. In such instances, the agency subsequently considers each panel's recommendations in determining whether the combination is appropriate for the relief of specific concurrent symptoms, is subject to the labeling requirements of more than one monograph, or whether special labeling is needed for the combination.

The data submitted to the Internal Analgesic Panel for its evaluation of the analgesic component of highly buffered aspirin for solution, an analgesic-antacid combination drug product, included the same information that had been submitted to the Antacid Panel. The agency concludes that it was appropriate for the Internal Analges Panel to reconsider some of the issu that the Antacid Panel had considere Furthermore, it is appropriate for the agency to consider recommendations from both Panels, as well as the comments and reply comments received in response to the Internal Analgesic Panel's recommended monograph.

96. Two comments stated that because most consumers do not know that a popular OTC highly buffered aspirin for solution product contains aspirin, they are unaware of the potential risks in using this product.

The comments provided no evidence to support the statement that "most consumers" are unaware of the presence of aspirin in the product to which they referred. Section 502(e) (1) of the act (21 U.S.C. 352(e)) requires that the labeling of all OTC drugs contain the established name of each active ingredient in the product. In addition, consumers are alerted to the potential side effects of aspirin-containing products by the label warnings proposed for such products in this tentative final monograph.

Section 502(c) of the act (21 U.S.C. 352(c)) also provides that information required to appear on the labeling be placed thereon prominently and with such conspicuousness as to render it likely to be read and understood by th ordinary individual under customary

conditions of purchase and use. The requirements for labeling ingredient information are spelled out more fully in the regulations at 21 CFR 201.10.

The agency believes that products labeled in accord with existing regulations and the requirements being established by this monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products will not present consumers with the potential problem described by the comments.

Q. Comment on Antihistamine-Analgesic Combinations

97. One comment argued that a currently marketed OTC drug product containing acetaminophen and phenyltoloxamine dihydrogen citrate is effective in treating tension headache and relieving musculoskeletal pain associated with anxiety and is more effective than acetaminophen alone in relieving pain. The comment mentioned studies by de Sola Pool (Ref. 1) and Gilbert (Ref. 2) that were submitted to the Panel. In response to the Panel's criticism of de Sola Pool's study, the comment submitted Drummond's reanalysis of this study (Ref. 3) and an independent analysis of Wallenstein (Ref. 4). The comment also submitted the results of a new study conducted by Scheiner (Ref. 5). The comment concluded that these studies show that phenyltoloxamine dihydrogen citrate in combination with acetaminophen should be classified as a Category I adjuvant.

The agency has reviewed the new data submitted and concludes that the data remain insufficient to support the effectiveness of phenyltoloxamine dihydrogen citrate as an analgesic adjuvant. The statistical reanalyses of the de Sola Pool study performed by Drummond (Ref. 3) and Wallenstein (Ref. 4) conclude that acetaminophen with phenyltoloxamine dihydrogen citrate is more effective than acetaminophen alone for the relief of headache. However, the study did not use a standardized scoring system to rate symptoms and the symptom complex being treated was not clearly defined. Therefore, the study is not acceptable as proof of the effectiveness of the ingredient as an analgesic adjuvant.

Gilbert's study (Ref. 2) did not show that the combination of acetaminophen and phenyltoloxamine dihydrogen citrate enhanced pain relief over acetaminophen alone. Drug differences were not detected until 48 hours after treatment started, an unacceptably long delay in a pain study. In addition, many pain states will spontaneously resolve over this period of time, and this effect may bias the study. There were a number of technical problems with the study, e.g., the patient population was too heterogeneous, and only 1 of 19 measures used for rating drug effects was concerned with pain. The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (address above) (Ref. 6).

The agency did not review the new study by Scheiner (Ref. 5) because the investigator was disqualified by FDA. The accuracy and reliability of the data from this study would need to be validated before the agency could accept this study in support of claims for the effectiveness of phenyltoloxamine dihydrogen citrate as an analgesic adjuvant.

Therefore, the agency proposes to classify phenyltoloxamine dihydrogen citrate as a Category III internal analgesic adjuvant in this tentative final monograph.

Regarding labeling, the agency proposes to classify as Category II any claims that represent or suggest relief of or treatment for tension or anxiety, including "for the treatment of tension headache." The agency proposes to classify such labeling claims as Category II because these claims imply the treatment of tension and anxiety rather than the amelioration of the pain that may be associated with such symptoms. In the final monograph for OTC daytime sedative drug products, the agency concluded that based on the available data any products labeled, represented, or promoted for indications such as "calmative," "soothes away the tension," and "calming down" are regarded as new drugs for which approved new drug applications would be required for marketing (44 FR 36380).

The Internal Analgesic Panel classified the term "nervous tension headache" in Category II (42 FR 35435). In its discussion of headache, the Panel identified the psychogenic headache as a major type of headache and stated that these "muscle contraction" or "tension headaches" may account for up to 90 percent of the chronic headaches seen by the physician. The Panel further recommended that the cause of chronic and recurrent headaches requires diagnosis by a physician. However, the Panel also stated that the occasional headache may be due to a variety of causes, including tension, and concluded that analgesics are safe and effective for the symptomatic relief of the occasional headache (42 FR 35352).

The agency concurs with the Panel that chronic and recurrent headaches require diagnosis by a physician. However, the agency also believes that consumers are familiar with headaches perceived to be due to tension. Because the warnings proposed in § 343.50(c) (1) and (2) of this tentative final monograph will adequately warn consumers against self-use of analgesics for pain that continues to persist, the agency has no objection to the use of the phrase "pain of tension headache" as acceptable additional information for the labeling of analgesic-containing products provided that additional words are not used that imply any treatment for tension or anxiety. Because the agency believes that the proposed indication "For the temporary relief of minor aches and pains associated with * * * headache * * *." is sufficiently broad to encompass headache from a variety of causes, the agency is not proposing to include the phrase "pain of tension headache" in its proposed indication for OTC internal analgesic drug products. This information may be included elsewhere in the labeling provided the phrase is not intermixed with labeling established by the monograph.

In addition, the Panel placed the claim "for the relief of musculoskeletal pain associated with anxiety" in Category II (42 FR 35486). The agency agrees with the Panel's classification because it believes that the term "musculoskeletal pain" is not readily understood by consumers. Furthermore, the agency is not aware of any OTC analgesic product labeled with such an indication. Therefore, the agency does not propose to include the claim "for the relief of musculoskeletal pain" in the monograph.

References

(1) De Sola Pool, N., "Analgesic/Calmative Effects of Acetaminophen and Phenyltoloxamine in the Treatment of Simple Nervous Tension Accompanied by Headache," draft of unpublished paper, in OTC Volume 030155.

(2) Gilbert, M.M., "The Efficacy of Percogesic in Relief of Musculoskeletal Pain Associated with Anxiety," draft of unpublished paper, in OTC Volume 030154.

(3) Drummond, C., "Re-analysis of the Study, " 'Analgesic/Calmative Effects of Acetaminophen and Phenyltoloxamine in the Treatment of Simple Nervous Tension Accompanied by Headache'," draft of unpublished paper, Comment No. SUP-3, Docket No. 77N-0094, Dockets Management Branch.

(4) Wallenstein, S.L., "Statistical Evaluation of Clinical Protocol Associates Study," draft of unpublished paper, Comment No. SUP-3, Docket No. 77N-0094, Dockets Management Branch.

(5) Scheiner, J.J., "The Efficacy of Percogesic in Treating Anxiety Caused by Musculoskeletal Trauma," draft of unpublished paper, Comment No. SUP03, Docket No. 77N-0094, Dockets Management Branch.

(6) Letter from W.E. Gilbertson, FDA, to E.B. Adams, Endo Laboratories, Inc., coded ANS 80/11/17 to C00045 and SUP003, Docket No. 77N-0094, Dockets Management Branch.

R. Comments on Data Required for Evaluation

98. Several comments objected to the Panel's recommended aspirin tablet dissolution-testing procedure (42 FR 35488). One comment questioned the applicability of the procedure for any use other than quality control because of the variable results that can be obtained. A few comments criticized the methodology, such as the dissolution medium and the apparatus, and noted the disparity between the Panel's recommended dissolution-testing procedure and that of the United States Pharmacopeial Convention (USPC). Other comments stated that the procedure did not provide for combination drug products containing aspirin.

The Panel concluded that "significant variation in dissolution rate and absorption rate between aspirin products demonstrates the need for a standard dissolution test which can be used to detect preparations which will be so slowly absorbed as to potentially increase local adverse effects on the gastric mucosa or decrease therapeutic effects due to decreased bioavailability" (42 FR 35374). Therefore, the Panel recommended its testing procedure to elicit public comments for the development of a dissolution standard for aspirin tablets that would assure that these drug products are properly formulated. Since the Panel's report was published, the agency and the USPC have worked to develop a dissolution standard for aspirin tablets and capsules. Dissolution tests for aspirin capsules, aspirin tablets, and buffered aspirin tablets have become official in the U.S.P. (Refs. 1, 2, and 3). The agency is proposing to require this dissolution testing in new § 343.90.

Dissolution tests have also become official in the U.S.P. for acetaminophen and aspirin tablets (Ref. 4) and for combination drug products containing aspirin, alumina, and magnesia (Ref. 5). The agency is also proposing to require this testing in new § 343.90. Dissolution tests for other OTC aspirin combination drug products have not yet been formulated, and FDA is deferring to the USPC to develop compendial dissolution standards for such combinations. As appropriate tests are developed, FDA intends to propose to require them as part of this monograph or related monographs. Until appropriate dissolution standards are in place, other OTC aspirin combination products are classified as Category III. Interested persons are invited to submit data in support of appropriate dissolution tests for any such combination products for potential inclusion in the final monograph.

References

(1) "United States Pharmacopeia XXI—National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 77, 1985.

(2) "United States Pharmacopeia XXI—National Formulary XVI," Supplement 4, United States Pharmacopeial Convention, Inc., Rockville, MD, 2130, 1986.

(3) "United States Pharmacopeia XXI—National Formulary XVI," Supplement 4, United States Pharmacopeial Convention, Inc., Rockville, MD, 2131, 1986.

(4) "United States Pharmacopeia XXI—National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 14, 1985.

(5) "United States Pharmacopeia XXI—National Formulary XVI," Supplement 2, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 1812 and 1813, 1985.

99. Noting that the Panel's recommended monograph contains no guidelines for studies needed to reclassify enteric-coated aspirin from Category III to Category I, one comment submitted proposed guidelines for studies to demonstrate the bioavailability of aspirin in an enteric-coated dosage form. The guidelines referred to an in vitro dissolution methodology for enteric-coated tablets, which the comment stated will be published in the U.S.P., and included a general proposal for designing a clinical protocol to test the bioavailability of enteric-coated aspirin. Two comments also submitted clinical protocols for bioavailability studies for enteric-coated aspirin products and requested that the protocols be approved by FDA for reclassifying enteric-coated aspirin from Category III to Category I.

The agency is aware that in vitro dissolution methodology for enteric-coated aspirin tablets and capsules has now been included in the U.S.P. (Ref. 1). However, the "enteric-coated" designation has been deleted in the U.S.P., and the products are now referred to as "Aspirin Delayed-Release Tablets" and "Aspirin Delayed-Release Capsules." FDA believes that the newly adopted U.S.P. test is an appropriate standard to support the reclassification of enteric-coated aspirin products from Category III to I. Therefore, the agency is proposing to include this dissolution test in the internal analgesic tentative final monograph in new § 343.90(c).

The agency had previously responded to the comments' clinical protocols for bioavailability studies (Refs. 2 and 3). Copies of these responses are on file in the Dockets Management Branch (address above). The need for bioavailability studies is superseded the methodology recently included U.S.P.

The agency proposes that any other enteric-coated analgesics, e.g., sodium salicylate, remain in Category III until adequate specifications are established for these products.

References

(1) "United States Pharmacopeia XXI—National Formulary XVI," Supplement 3, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 1972 and 1973, 1985.

(2) Letter from W.E. Gilbertson, FDA, to D. Marcus, Norcliff Thayer Inc., coded LET009 to C00109, Docket No. 77N-0094, Dockets Management Branch.

(3) Letter from W.E. Gilbertson, FDA, to E.J. Hiross, Sterling Drug Inc., coded ANS to C00110, Docket No. 77N-0094, Dockets Management Branch.

100. One comment, noting that the Panel recommended a dissolution test for plain as well as buffered aspirin tablets (42 FR 35488), expressed concern that there is no provision for a comparable test method for aspirin powder dosage forms.

The agency points out that the statement to which the comment referred is in the Panel's discussion tablet dosage forms (42 FR 35374), in which the Panel expressed concern about significant variations in dissolution rate and absorption rate buffered and unbuffered aspirin tablets. This concern prompted the Panel to recommend a dissolution test for aspirin tablets (buffered and unbuffered). The Panel did not recommend a dissolution test for powders because it concluded that they are rapidly absorbed and often reach peak blood levels more rapidly than the tablet dosage form (42 FR 35376).

As stated in comment 98 above, the agency is proposing to include in new § 343.90 of the internal analgesic tentative final monograph all of the dissolution tests for aspirin products that are in the U.S.P. There are no official dissolution tests for aspirin powders. Based on the Panel's discussion of powders and the fact that the agency is unaware of any problems of absorption with aspirin powders, the agency concludes that dissolution testing is not needed for either buffered or unbuffered aspirin powders.

101. One comment observed that the Panel's recommended buffered aspirin acid-neutralizing testing procedure (42 FR 35487) did not provide for the removal of aspirin. The comment stat that because aspirin interferes with th

assay, it should be removed before determining the buffering capacity.

The agency disagrees with the comment's suggestion that aspirin be removed from buffered aspirin drug products before testing their acid-neutralizing capacity. As stated in § 343.10(b)(2) of this tentative final monograph, the finished product must provide 1.9 mEq of acid-neutralizing capacity, which exceeds the amount needed to neutralize the aspirin. Therefore, no provision for the removal of aspirin is needed in the testing procedure.

102. One comment pointed out that measurement of the acid-neutralizing capacity of combination drug products containing buffered aspirin and other active ingredients may require modifications in the standard method used for testing buffered aspirin products in § 331.25.

The comment did not provide any specific examples of needed modifications. However, the agency has revised § 331.29 to establish a mechanism for requesting specific modifications in the test procedure. This revision was published as a final rule in the Federal Register of August 31, 1982 (47 FR 38480) and states that any proposed modification and the data to support it should be submitted as a petition according to § 10.30. The revision further provides for a redelegation of authority to grant or deny such petitions in order to facilitate prompt action.

S. Comments on Additional Ingredients for Monograph

103. One comment requested that the lysine salt of aspirin, which has been marketed in a number of countries for several years, be included in the tentative final monograph with an indication for the temporary relief from occasional minor aches, pains, and headaches. The comment provided information on the chemical and physical properties, toxicity, bioavailability, pharmacokinetics, and gastrointestinal tolerance of a lysine aspirin product. The comment stated that lysine aspirin is a readily soluble salt of aspirin that dissociates in water into lysine and acetylsalicylic acid, that the product is intended for solution in water prior to administration, and that acetylsalicylic acid is the active moiety that exists in the gastrointestinal tract and is absorbed.

The agency has determined that the lysine salt of aspirin is a "new drug" as defined in section 201(p)(2) of the act (21 U.S.C. 321(p)(2)) as follows:

> Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

FDA interprets the terms "material extent" and "material time" to mean availability in the United States marketplace. The agency is unaware that lysine aspirin has ever been marketed as a drug in the United States. The comment provided no evidence to show otherwise. Thus, the agency regards this ingredient to be a new drug, requiring an approved application prior to OTC marketing.

104. One comment submitted information on calcium salicylate and requested that it be included as an analgesic ingredient in the tentative final monograph.

The Panel did not review calcium salicylate because no data were submitted on this ingredient. The comment provided information on the historical use, physical properties, and chemical preparation of calcium salicylate, but supplied no evidence that it has been marketed in the United States and provided no substantive data to demonstrate the safety and effectiveness of this ingredient as an OTC analgesic-antipyretic. FDA is not aware that calcium salicylate has ever been marketed as an OTC analgesic-antipyretic in the United States. Thus, calcium salicylate falls within the definition of a new drug within the meaning of section 201(p) of the act, as discussed in comment 103 above, and requires an approved application prior to marketing as an OTC analgesic-antipyretic drug.

The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 1).

Reference

(1) Letter from W.E. Gilbertson, FDA, to C. Schreur, Schreur Investments Inc., coded LET026 Docket No. 77N-0094, Dockets Management Branch.

105. One comment to the Miscellaneous Internal Panel requested that potassium salicylate be included as a Category I ingredient for use in OTC menstrual drug products. The comment argued that potassium salicylate is a naturally occurring substance and is equivalent to sodium salicylate and salicylic acid in terms of salicylate activity.

The comment did not include any data on this ingredient nor were any submitted to the Miscellaneous Internal Panel or to the Internal Analgesic Panel. The agency is aware that potassium salicylate has been marketed in the United States as an ingredient in OTC and prescription analgesic drug products (Refs. 1 through 6). Until data on potassium salicylate are submitted for review, however, the agency has an insufficient basis to consider further the request to include this ingredient in an OTC drug monograph. Based on its marketing history, potassium salicylate is classified as Category III in this tentative final monograph.

References

(1) Van Tyle, W.K., "Chapter 10—Internal Analgesic Products," *in* "Handbook of Nonprescription Drugs," 5th Ed., American Pharmaceutical Assoc., Washington, pp. 132–133, 1977.

(2) Van Tyle, W.K., "Chapter 10—Internal Analgesic Products," *in* "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Assoc., Washington, p. 204 and p. 367, 1982.

(3) Korbethy, S.H., C.A. Sohn, and R.P. Tannenbaum, "Chapter 17—Menstrual Products," *in* "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Assoc., Washington, p. 367, 1982.

(4) Sohn, C.A., B.H. Korbethy, and R.P. Tannenbaum, "Chapter 17—Menstrual Products," *in* "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Assoc., Washington, p. 382, 1986

(5) Billings, N.F., and S.M. Billings, editors, "American Drug Index," 31st Ed., J.B. Lippincott Co., Philadelphia, p. 495, 1987.

(6) Huff, B.B., editor, "Physicians' Desk Reference," 41st Ed., Medical Economics Co., Inc., Oradell, NJ, p. 1631, 1987.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all the claimed active ingredients submitted to the Internal Analgesic and Miscellaneous Internal Panels, as well as other data and information available at this time, and concurs with the Panels' categorization of ingredients. In addition, the agency has reviewed three ingredients not reviewed by the Panels. For the convenience of the reader, the following table is included as a summary of the categorization of analgesic-antipyretic active ingredients by the Panels and the proposed classification by the agency.

Analgesic-antipyretic active ingredients	Panels	Agency
Acetaminophen	I	I
Acetanilide [1]	II	II

Analgesic-antipyretic active ingredients	Panels	Agency
Aluminum aspirin	III	III
Antipyrine	III	III
Aspirin	I	I
Calcium salicylate	(2)	(3)
Carbaspirin calcium	I	I
Choline salicylate	I	I
Codeine	II	II
Iodoantipyrine [4]	II	II
Lysine aspirin	(2)	(3)
Magnesium salicylate	I	I
Potassium salicylate	(2)	III
Phenacetin	II	II
Quinine	II	II
Salicylamide	III	III
Salsalate	III	III
Sodium salicylate	I	I

[1] Formerly acetanilid.
[2] Not reviewed by the Internal Analgesic or Miscellaneous Internal Panels.
[3] Determined by the agency to be a "new drug."
[4] Identified by the Panel as iodopyrine.

After reviewing the available data and information, the agency has concluded that the Internal Analgesic Panel's categorization of ingredients for safety and effectiveness as analgesic-antipyretic adjuvants will remain unchanged, except for methapyrilene fumarate. The agency's reasons for recategorizing methapyrilene salts are presented in paragraph B. 32 below.

The following table is included as a summary of the categorization of analgesic-antipyretic adjuvant ingredients.

Analgesic-antipyretic adjuvants	Panel	Agency
Aminobenzoic acid	II	II
Caffeine	III	III
Methapyrilene fumarate	III	II
Pheniramine maleate	III	III
Phenyltoloxamine dihydrogen citrate	III	III
Pyrilamine maleate	III	III
Salicylamide	III	III
Sodium para-aminobenzoate	II	II

The tables above do not address antirheumatic use, which appears only in professional labeling. The tables also do not address dosage forms, such as timed-release products, rectal suppositories, and enteric-coated aspirin. These dosage forms are discussed in comments 78, 79, and 99 above.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for analgesic, antipyretic, and antirheumatic drug products (42 FR 35444, 35453, 35468, and 35467). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them unless otherwise noted in this document. (See comments 85, 88, 89, 91, 93, 97, 98, and 101 above.)

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any internal analgesic, antipyretic, or antirheumatic ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The Panel recommended as a statement of indications for OTC analgesic drug products: "For the temporary relief of occasional minor aches, pains and headache," and as a statement of indications for OTC antipyretic drug products: "For the reduction of fever." The agency is expanding and combining these statements to allow the inclusion of representative types of pain and causes of fever that are amenable to OTC treatment. (See comments 15, 16, and 17 above.) Accordingly, the statements in §§ 343.50(a) (2) and (3) are being deleted, and the labeling statement recommended in § 343.50(a)(1) is being changed to the following statement in this tentative final monograph (§ 343.50(b)(1)): "For the temporary relief of minor aches and pains" [which may be followed by one or more of the following: ["associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea)"), or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)"))], ("and for the minor pain from arthritis"), and ("and to reduce fever.")] The agency is also proposing to include "flu" as an indication for analgesic-antipyretic products containing acetaminophen. In addition, the agency is proposing that an OTC analgesic-antipyretic drug product may be identified as a "pain relief," "analgesic (pain reliever)," "pain reliever-fever reducer," or "analgesic (pain reliever)-antipyretic (fever reducer)" (§ 343.50(a)).

2. The agency is proposing combined analgesic-antipyretic labeling for analgesic-antipyretic drug products labeled only for use in children, e.g., children's acetaminophen. Based upon representative types of pain and causes of fever that are amenable to OTC treatment in children over 2 years of age, the indications statement for OTC children's analgesic-antipyretic drug products is being proposed as follows (§ 343.50(b)(2)): "For the temporary relief of minor aches and pains" [which may be followed by: ["associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," or "toothache")] and/or ("and to reduce fever.")] The agency is also proposing to include "flu" as an indication in the labeling of products that contain acetaminophen. (See comments 15 and 16 above.)

3. The agency is proposing in §§ 343.50 (c)(1)(ii) and (c)(2)(ii) of this tentative final monograph that internal analgesic drug products labeled for the relief of sore throat pain bear a modified version of the warning statement currently recommended in 21 CFR for "throat preparations for temporary relief of minor sore throat: Lozenges, troches, washes, gargles, etc." (See comment 15 above.) In the tentative final monograph for OTC oral health care drug products, the agency has proposed to remove the existing recommended warning statement in § 369.20 as well as the suggested warning for OTC drugs for minor sore throats in § 201.315. (See 53 FR 2456.)

4. The warnings recommended by the Panel in §§ 343.50(c)(1) (i) and (ii) are being revised and proposed as three warnings as follows in § 343.50(c):

(1) *For products labeled for adults*—(i) *For products containing any ingredient in § 343.10.* "Do not take this product for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition."

(2) *For products labeled for children 2 years to under 12 years of age*—(i) *For products containing any ingredient in § 343.10.* "Do not give this product for pain for more than 5 days or for fever more than 3 days unless directed by doctor. If pain or fever persists or get worse, if new symptoms occur, or if redness or swelling is present, consult

doctor because these could be signs of a serious condition."

(3) *For products labeled both for adults and for children 2 years to under 12 years of age.* * * * "Do not take this product for pain for more than 10 days (for adults) or 5 days (for children), and do not take for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. Do not give this product to children for the pain of arthritis unless directed by a doctor."

These warnings are being revised for clarity, to distinguish between products used by adults and/or children, and to alert consumers to appropriate time limitations on self-treatment with OTC analgesic-antipyretic drug products as well as to symptoms that require professional treatment. (See comments 13, 14, 18, and 30 above.)

5. Because the agency is combining the indications for pain and fever into a single statement and because dosage schedules are the same for analgesic and antipyretic ingredients, the agency is proposing a single dosage schedule in § 343.50(d) for each analgesic-antipyretic ingredient. (See comments 16 and 53 above.) Section § 343.10 is being revised to list all active ingredients, and § 343.12 and 343.14 are being deleted.

6. The agency is proposing deletion of the warning recommended in § 343.50(c)(5)(ii) because consumers might interpret it to mean that acetaminophen can be used to treat arthritis. The agency is also proposing deletion of the warning recommended for aspirin in § 343.50(c)(3)(i) because the agency is concerned that different labeling statements on acetaminophen and aspirin products concerning arthritis might encourage consumers to self-diagnose and self-treat arthritis. (See comment 19 above.)

7. The agency is proposing the following in § 343.50(b)(4)(i) to provide for children's labeling: *For products labeled only for children 2 to under 12 years of age containing any ingredient identified in § 343.10.* (A) The labeling of the product contains, on the principal display panel, either of the following:

(*1*) "Children's (*trade name of product or generic name of ingredient(s)*)."

(*2*) "(*Trade name of product or generic name of ingredient(s)*) for Children."

(B) The labeling for adults in § 343.50(d) and the statement "Children to under 12 years of age" in § 343.50(d)(3)(ii) are not required. (See comment 30 above.)

8. The following are agency initiated changes in the Panel's recommended monograph based on the format and style of recently published monographs:

(a) The signal word "warning" has been used routinely in all labeling in OTC drug monographs instead of the signal word "caution." Accordingly, the word "caution" is not being included in § 343.50(c)(1)(v) (B) and (C) in this proposed monograph. (See comment 32 above.)

(b) The definition section contains only one definition: analgesic-antipyretic drug. Other definitions appearing in the advance notice of proposed rulemaking are not considered necessary for this tentative final monograph.

(c) The agency is redesignating proposed Subpart D of the monograph as Subpart C, placing the labeling sections under Subpart C.

(d) In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and other applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

9. The agency is proposing to delete the first sentence of the aspirin hypersensitivity warning recommended in § 343.50(c)(4)(i) (redesignated § 343.50(c) (1)(iv)(A) and (2)(iv)(A)), "This product contains aspirin." (See comment 33 above.) This sentence is unnecessary because section 502(e)(1) of the act (21 U.S.C. 352(e)(1)) requires all drug products to bear on the label the established name of the active ingredient or ingredients contained in the product.

10. The agency is proposing that the warning recommended in § 343.50(c)(3)(v) (redesignated § 343.50(c)(1)(v)(C)) be identified as a drug interaction precaution (see comment 36 above) as follows: "*Drug Interaction Precaution.* Do not take this product if you are taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis unless directed by a doctor." This precaution is being modified in § 343.50(c)(2)(v)(C) for products labeled for children 2 years to under 12 years of age. For products labeled both for adults and children, the precaution for adults will apply. (See § 343.50(c)(3).)

11. The agency is revising the warning recommended in § 343.50(c)(3)(ii) (redesignated § 343.50(c) (1)(v)(A) and (2)(v)(A)) to read: "If ringing in the ears or a loss of hearing occurs, consult a doctor before taking any more of this product." The agency believes this wording more clearly conveys the appropriate course of action to the consumer. (See comment 39 above.)

12. The statements recommended by the Panel in § 343.50(c)(3)(iii) (*a*) and (*b*) are being moved to § 343.50(d)(3) (i) and (ii) in the tentative final monograph because they are directions for use, not warnings. (See comment 41 above.)

13. The agency is proposing deletion of the term "stomach distress" from § 343.50(c)(3)(iv) (redesignated § 343.50(c)(1)(v)(B)) and is revising the warning as follows: "Do not take this product if you have stomach problems (such as heartburn, upset stomach, or stomach pain) that persist or recur, or if you have ulcers or bleeding problems, unless directed by a doctor." This warning is being further revised in § 343.50(c)(2)(vi)(B) for products labeled for children 2 years to under 12 years of age. For products labeled for both adults and children, the warning for adults will apply. (See § 343.50(c)(3). See also comment 31 above.)

14. The Panel classified the claims "acts five times faster than aspirin" and "reaches peak action twelve times faster than aspirin" in Category II for choline salicylate. However, the agency finds a reasonable basis to classify such claims in Category III. (See comment 45 above.) This classification is consistent with the Panel's treatment of similar claims for buffered aspirin, i.e., the data are not sufficient to support such claims as "faster to the bloodstream than plain aspirin."

15. The agency finds that labeling claims such as "extra-strength," "extra pain relief," "maximum strength," and "arthritis strength" are outside the scope of the OTC drug review. (See comment 48 above.)

16. The Panel recommended a children's dosage unit of 80 mg for aspirin and acetaminophen. The agency is proposing that the children's dosage unit for aspirin, acetaminophen, and sodium salicylate be 80 mg or 81 mg because both strengths are marketed, and the difference between these strengths is of no therapeutic consequence. In addition, a minimal effective dose for children over 9 years of age (i.e., 320 mg for the 80-mg dosage unit, 324 mg for the 81-mg dosage unit, or 325 mg for the 325-mg dosage unit) is being added to the children's dosage schedule. (See comment 58 above.)

17. Quantities of active ingredients are expressed in the tentative final

monograph in metric units only. Manufacturers may voluntarily list quantities of active ingredients in both apothecary and metric units. (See comment 80 above.)

18. The agency is not adopting the analgesic equivalence value labeling statements recommended by the Panel in § 343.50(e) because they do not appear to serve their intended purpose and could be confusing to consumers. (See comment 56 above.)

19. The statements on dosage units recommended in § 343.50(d) are also being deleted in this tentative final monograph. The agency believes that the terms "standard" and "nonstandard" would not serve their intended purpose of simplifying comparisons among various products and may confuse consumers. (See comment 53 above.)

20. The dosage schedules for aspirin, acetaminophen, and sodium salicylate recommended by the Panel in § 343.10 (a), (b), and (f) are being revised to eliminate the concepts of "standard" and "nonstandard" schedules and are being combined under § 343.50(d)(2). (See comment 53 above.) In accordance with the agency's changes discussed in this paragraph and in paragraph number 18 above, the Panel's recommended definitions in § 343.3 (c), (m), and (p) are not being included in this tentative final monograph.

21. The agency concurs with the Panel's recommendation on dosages of aspirin, acetaminophen, and sodium salicylate for adults and has incorporated this information in the directions section of the tentative final monograph (§ 343.50(d)), except that the agency is not including in the tentative final monograph a maximum initial dose of 975 mg for these ingredients when given in a 4-hour dosage regimen. (See comments 53 and 63 above.)

22. The Panel recommended a dosage of 325 to 650 mg magnesium salicylate every 4 hours, based upon data submitted on a product containing 325 mg of the tetrahydrate form of magnesium salicylate. This is the same as the dosage range established for sodium salicylate. However, the agency has determined that 377 mg magnesium salicylate tetrahydrate, and not 325 mg, is equivalent to 325 mg sodium salicylate. Given a minimum effective dosage of 325 mg sodium salicylate, the dosage of magnesium salicylate tetrahydrate that would contain an equivalent amount of salicylic acid is 377 mg. Therefore, the agency concludes that the minimum effective dosage of magnesium salicylate should be 377 mg, and the maximum dosage for this ingredient should be 754 mg. The dosages for magnesium salicylate are being revised accordingly, and this tentative final monograph specifies in § 343.50(d)(6) that the dosages are based on the tetrahydrate form of magnesium salicylate. (See comment 64 above.)

23. The agency is not including analgesic-antipyretic combinations that contain only salicylates in this monograph because such combinations are not in accordance with general OTC combination drug product guidelines. (See comment 72 above.) However, the agency has expanded the allowable combinations recommended by the Panel by providing a range of acceptable amounts of active ingredients that may be contained in a combination product. The agency discussed combination products containing analgesic and cough-cold ingredients in § 341.40 of the cough-cold combinations tentative final monograph (53 FR 30522). Accordingly, the Panel's recommendations in § 343.20(d) (1), (2), (3), and (4) of its monograph are not being addressed in this tentative final monograph, and appropriate cross-references to Part 341 are being included. (See comment 67 above.)

24. Based on the recommendations of the Miscellaneous Internal Panel, the agency has expanded the combination section of the monograph to provide for allowable combinations of analgesic ingredients or combinations of analgesic ingredients with a diuretic when the product is labeled for "menstrual" claims. (See the tentative final monograph for OTC menstrual drug products published elsewhere in this issue of the Federal Register.)

25. The agency notes that the Panel concluded that OTC acetaminophen products for children should be packaged in containers containing no more than 36 tablets (42 FR 35415). This recommendation was based on an existing regulation recommending a 36-tablet limitation of 1¼ gr children's aspirin tablets in § 201.314(c)(2) (21 CFR 201.314(c)(2)) and not on data pertaining to the toxicity of acetaminophen in children. No comments were submitted in response to the Panel's recommendation. The agency has evaluated currently marketed pediatric acetaminophen products (Ref. 1) and does not believe it necessary to include this packaging limitation in the tentative final monograph. The agency specifcally invites comments on the need for a regulation to limit the number of dosage units per container for pediatric dosage forms of acetaminophen in light of child proof closures and the degree of voluntary compliance in effect at this time among the manufacturers of these products. The agency also invites comments on the need for a regulation requiring the 36-tablet limitation for pediatric aspirin products which is recommended in 21 CFR 201.314(c)(2).

Reference

(1) Cardinale, V.A., Editor, "1987 Redbook," Medical Economics Company Inc., Oradell, NJ. pp. 100–103, 130, 253, 452, 563, 600, 1987.

26. The agency is changing the Panel's recommended single dose of 65 mg caffeine to 75 mg caffeine as an analgesic adjuvant, not to exceed a single adult dose of 150 mg or a maximum daily dose of 600 mg. Caffeine remains in Category III as an analgesic adjuvant. However, industry has responded to FDA's concern and provided additional data which are currently under review by the agency. (See comment 92 above.)

27. The agency is proposing to include by reference the dissolution testing procedures for aspirin capsules, as contained in U.S.P. XXI at page 77, for aspirin tablets as contained in U.S.P. XXI Supplement 4 at page 2130, and for buffered aspirin tablets, as contained in U.S.P. XXI Supplement 4 at page 2131, as part of this tentative final monograph. (See comment 98 above.) Furthermore, the agency is also including by reference the dissolution standard for acetaminophen and aspirin tablets as contained in U.S.P. XXI at page 14, the dissolution standard for one aspirin combination product as contained in U.S.P. XXI Supplement 2 at pages 1812 and 1813, and the dissolution standard for enteric coated aspirin tablets (delayed-release tablets) as contained in U.S.P. XXI Supplement 3 at pages 1972 and 1973. (See comments 98 and 99 above.)

28. The agency is deleting the Panel's recommended definition for buffered aspirin in § 343.3(j) and is including the definition in the active ingredients section (§ 343.10(b)(2)) of this tentative final monograph as a result of the establishment of a U.S.P. monograph for buffered aspirin tablets in U.S.P. XXI Supplement 4 at page 2131. The definition of buffered aspirin in § 343.10(b)(2) of this tentative final monograph is being proposed as follows: Buffered Aspirin "Aspirin identified in paragraph (b)(1) of this section may be buffered with any antacid ingredient(s) identified in § 331.11 provided that the finished product contains at least 1.9 milliequivalents of acid-neutralizing capacity per 325 milligrams in accordance with § 331.26." (See comments 42 and 77 above.)

29. The agency is deleting the Panel's recommended definition in § 343.3(k) because the same information is

contained in § 343.20(d)(6) (see comment 76 above) which is being redesignated 343.20(b)(3) in this tentative final onograph and is being revised to include all products containing aspirin with antacid as follows: "Aspirin identified in § 343.10(b)(1) may be combined with any antacid ingredient identified in § 331.11 or any combination of antacids permitted in accordance with § 331.10(a) provided that the finished product meets the requirements of § 331.10, is marketed in a form intended for ingestion as a solution, and bears labeling indications in accordance with § 343.60(b)(4)."

In addition, the agency is proposing that such products be identified as follows: "pain reliever/fever reducer" (or the variation permitted in § 343.50(a)) and "antacid." (See comments 42 and 76 above.)

30. The agency is proposing indications for products containing aspirin with antacid that are based upon the aspirin indications for pain and fever in § 343.50(b)(1) and the antacid indications in § 331.30(b). (See comment 47 above.)

31. The labeling for products containing acetaminophen with antacid (acetaminophen and antacid combinations), provided for in recommended § 343.20(d)(5) and designated § 343.20(b)(1) in this ntative final monograph, is being nodified to include a statement of dentity and the revised indications labeling in § 343.60. (See comment 47 above.)

32. The agency is including in § 343.80 proposed professional labeling on the use of aspirin, buffered aspirin, or aspirin in combination with an antacid in the prevention of myocardial infarction in patients with a previous infarction or unstable angina pectoris. The agency is also proposing to incorporate labeling on the use of aspirin and buffered aspirin without sodium for transient ischemic attacks. (See comments 49 and 50 above.)

A number of other professional labeling indications also are being proposed in § 343.80(a) of the tentative final monograph. The agency is aware that some manufacturers have included statements in the labeling of their internal analgesic-antipyretic drug products that advise consumers to see their doctor for other (or new) uses of aspirin (or name of product). Such information may be beneficial to consumers, and the agency has no objection to a general statement of this 'ype being included in the labeling of)TC internal analgesic-antipyretic drug)roducts. The agency is also aware that nformation about these other uses of these products has appeared in newspapers and magazines and on television and radio. The agency is concerned that consumers may read or hear this information and self-medicate with an OTC drug product for one of these conditions without consulting with their doctor. Consumers should not self-medicate with an OTC analgesic-antipyretic drug product for any of these professional indications, and use for any of these conditions should be only under a doctor's supervision because serious side effects may occur. The agency believes that it is important that any information provided to consumers about other (professional) uses of these products be accompanied by a counterbalancing statement that the consumer should not use the product for more than 10 days (consistent with the allowable OTC labeling being proposed in this tentative final monograph) without consulting their doctor because serious adverse effects may occur. Examples include possible bleeding and stroke.

Based upon these new uses of aspirin and recognizing the evolving nature of this issue, the agency is proposing the following optional statement in this tentative final monograph: "See your doctor for other uses of [insert name of ingredient or trade name of product], but do not use for more than 10 days without consulting your doctor because serious side effects may occur." The agency believes that such information should be provided to consumers in the most effective manner and should be prominently displayed in labeling so that it may readily be seen and understood. At this time, the agency is proposing this as optional (allowable) labeling. The agency invites comment on this statement or other alternative labeling, appropriate placement in labeling, and whether the 10 day limitation on use should be an integral part of any such statement. The agency also invites comment on whether this information should be part of the required labeling for these products.

33. The agency is not adopting the liver warning in § 343.50(c)(5)(i), but is proposing that one of the following overdose warnings appear on all acetaminophen products to follow those general overdose warnings required in § 330.1(g) (21 CFR 330.1(g)): for products labeled for adults (§ 343.50(c)(1)(iii)), "Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms" or for products labeled for children (§ 343.50(c)(2)(iii)), "Prompt medical attention is critical even if you do not notice any signs or symptoms." For products labeled for both adults and children, the warning for adults will apply, as described in § 343.50(c)(3). (See comment 25 above.)

34. The agency has reclassified methapyrilene fumarate from Category III to Category II as an OTC analgesic, antipyretic, and antirheumatic adjuvant ingredient. A tentative final rule for nighttime sleep-aids, published in the Federal Register of June 13, 1978 (43 FR 25544), proposed to place methapyrilene in Category II because of preliminary studies implicating this drug as a carcinogen, or a carcinogen synergist with nitrates, in rats. However, at that time, the studies were too preliminary to support a definitive finding of carcinogenicity for methapyrilene that would necessitate its immediate removal from all products in the OTC drug market.

On May 1, 1979, the agency received an interim report from the National Cancer Institute (NCI) regarding carcinogenicity studies performed with methapyrilene at the Frederick Cancer Research Center. The results of these studies have been published by Lijinsky, Reuber, and Blackwell (Ref. 1). The NCI interim report stated that methapyrilene is a potent carcinogen in rats and must be considered a potential carcinogen in man. FDA reviewed this report and concurred with its conclusions. In June 1979, the agency initiated a recall letter to all manufacturers holding an approved new drug application (NDA) for products containing methapyrilene. This voluntary recall has eliminated drug products containing methapyrilene from the marketplace. Products containing methapyrilene are now considered to be misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) and "new drugs" under section 201(p) of the act (21 U.S.C. 321(p)).

The agency received no comments on methapyrilene fumarate, which was classified as Category III by the Panel as an analgesic adjuvant. Based on the studies discussed above, the agency has reclassified methapyrilene fumarate from Category III to Category II.

Reference

(1) Lijinsky, W., M.D. Reuber, and B.N. Blackwell, "Liver Tumors Induced in Rats by Chronic Oral Administration of the Common Antihistamine Methapyrilene Hydrochloride," *Science*, 209:817–819, 1980.

35. The agency is expanding the Panel's recommended warning on salicylate allergy in § 343.50(c)(6) (redesignated § 343.50(c) (1)(v) and (2)(v)) to include aspirin in an effort to assure that consumers, most of whom are apt to be familiar with aspirin, will

understand that aspirin is also a salicylate and that the allergic reaction that they may associate with aspirin is a salicylate allergy and can be caused by any of the ingredients in this drug group.

36. The Panel was concerned with the effects of aspirin or carbaspirin calcium on increasing duration of labor, changing hemostatic mechanisms in the newborn and increasing maternal blood loss (42 FR 35404). The latter may be a hazard particularly in premature labor and thus at any time during the last 3 months of pregnancy. For these reasons, the Panel concluded that there is a potential hazard to the use of aspirin during pregnancy and recommended the following warning on all aspirin-containing products: "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician." The agency received no comments on this issue, but is expanding the Panel's labeling recommendation to inform consumers of the reason for the warning. In addition, in the Federal Register of December 3, 1982 (47 FR 54750), the agency published a final rule to amend the general drug labeling provisions in Part 201 by adding new § 201.63, which includes the following warning to pregnant and nursing women concerning the use of OTC drugs that are intended for systemic absorption: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product." Because of this more recent general warning, the agency is proposing that the following revised warning follow the warning required in § 201.63(a): "IMPORTANT: Do not take this product during the last 3 months of pregnancy unless directed by a doctor. Aspirin taken near time of delivery may cause bleeding problems in both mother and child."

37. After reviewing the conclusions stated in three Panel reports (Oral Cavity at 42 FR 22796, Internal Analgesic at 42 FR 35376, and Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment at 44 FR 69845) concerning aspirin's ability to exert a topical effect as well as the available data, the agency concluded that there are not sufficient data available to permit final classification of aspirin as a topical analgesic/anesthetic in the tentative final monograph for OTC oral health care drug products, published in the Federal Register of January 27, 1988 (53 FR 2436). In that tentative final monograph, the agency deferred the systemic effectiveness of aspirin in a chewing gum dosage form for the relief of many kinds of pain including sore throat to this rulemaking (53 FR 2442). Although the topical analgesic effect of aspirin is not being specifically addressed in this rulemaking, the agency tentatively accepts the conclusion of the majority of the Oral Cavity Panel and the Internal Analgesic Panel that aspirin in a chewing gum base is safe for the relief of sore throat pain when labeled with adequate directions and warnings against misuse.

Although the Internal Analgesic Panel concluded that the topical effect of aspirin or any analgesic in a chewing gum dosage form has not been adequately tested for the treatment of sore throat pain, it found the marketing of an OTC analgesic in a chewing gum formulation acceptable for its systemic analgesic effect if the product provides the minimum effective dose (325 to 650 mg aspirin/dose) and is labeled according to the Panel's proposed monograph. The Panel also stated its concern about the possibility of oral mucosal damage and the effect of aspirin on blood clotting after oral surgery or tonsillectomy and recommended that the labeling of such product formulations include the warning, "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician." The Panel further recommended that aspirin for a local topical effect be deferred to the Oral Cavity Panel for evaluation (42 FR 35376).

The Oral Cavity Panel concluded that OTC anesthetic/analgesic ingredients are useful for the treatment of the symptoms of occasional minor sore throat and mouth but was divided in its conclusions about the safety and effectiveness of aspirin as an anesthetic/analgesic ingredient for topical use on the mucous membranes of the mouth and throat (47 FR 22769 and 22796). The majority of the Panel concluded that aspirin incorporated in a chewing gum base is safe and effective as an OTC anesthetic/analgesic ingredient for topical use on the mucuous membranes of the mouth and throat. However, the minority of the Panel concluded that there were insufficient data available to permit final classification of the safety and effectiveness of aspirin as an OTC anesthetic/analgesic ingredient. The minority of the Panel had reservations about the safety of topically applied aspirin used in the oral cavity and believed that aspirin has no known topical anesthetic or analgesic activity. It also believed that any analgesic effect from aspirin applied topically in the oral cavity is ultimately due to systemic absorption and not to topical application. Both the majority and minority of the Panel concluded that aspirin should not be used following operative procedures of the mouth or throat.

Because the agency is aware that aspirin increases bleeding time and inhibits platelet aggregation (42 FR 35384 and 47 FR 22797) and because aspirin-related hemorrhage after oral surgery and tonsillectomy is a well documented occurrence (Refs. 1, 2, and 3), the agency agrees with both the Internal Analgesic and Oral Cavity Panels that aspirin in a chewing gum form or chewable tablet form should not be used for at least 7 days after oral surgery or tonsillectomy (42 FR 35377 and 47 FR 22798 and 22801). The agency is therefore proposing the following warning for these dosage forms of aspirin: "Do not take this product for at least 7 days after tonsillectomy or oral surgery unless directed by a doctor."

References

(1) Hersh, R.A., "A Clinical Study Comparing the Incidence of Postoperative Bleeding in Patients Using Salicylate Containing Analgesics Versus Acetaminophen Analgesics," *The Bulletin of the Bergen County Dental Society*, 40:6–5 and 16, 1974.

(2) Reuter, S.H., and W.W. Montegomery, "Aspirin vs Acetaminophen After Tonsillectomy," *Archives of Otolaryngology*, 42:214–217, 1964.

(3) Singer, R., "Acetylsalicylic Acid: A Probable Cause for Secondary Tonsillectomy Hemorrhage," *Archives of Otolaryngology*, 42:19–20, 1945.

38. Section 201.314 (21 CFR 201.314) sets forth certain labeling requirements regarding warnings on OTC drug products containing salicylates and statements of policy on labeling such drugs. Several provisions of § 201.314 may be superseded by the requirements established in several OTC drug final monographs (e.g., internal analgesic, external analgesic, and overindulgence in alcohol and food). When those monographs are finalized, the agency will revise the appropriate portions of § 201.314. In addition, the agency may incorporate some of the requirements of § 201.314 into the appropriate monographs.

In addition, the agency is proposing to remove paragraph (a)(1) of § 310.201 and reserve paragraph (a)(1) for future use. The provisions of § 310.201(a)(1) will be superseded by the requirements of the internal analgesic final monograph. For the same reason, those portions of §§ 369.20 and 369.21 applicable to salicylates and acetaminophen are also proposed for removal.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC internal analgesic, antipyretic, and antirheumatic drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any impact that this rulemaking would have on OTC internal analgesic, antipyretic, and antirheumatic drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC internal analgesic, antipyretic, and antirheumatic drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on internal analgesic, antipyretic, and antirheumatic drug products, a period of 180 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(c)(6) this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Sections 343.50(c)(1)(viii)(A) and 343.50(c)(2)(viii)(A) of this proposed rule contain collection of information requirements. As required by section 3504(h) of the Paperwork Reduction Act of 1980, FDA has submitted a copy of this proposed rule to the Office of Management and Budget (OMB) or its review of these collection of information requirements. Other organizations and individuals desiring to submit comments on the collection of information requirements should direct them to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Rm. 3208, New Executive Office Bldg., Washington, DC 20503. Attn: Shannah Koss.

Interested persons may, on or before May 16, 1989, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before May 16, 1989. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the Federal Register.

Interested persons, on or before November 16, 1989, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before January 16, 1990. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on January 16, 1990. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Prescription exemption.

21 CFR Part 343

Internal analgesics, Labeling, Over-the-counter drugs.

21 CFR Part 369

Labeling, Over-the-counter drugs, Warning and caution statements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR Part 310 is revised to read as follows:

Authority: Secs. 501, 502, 503, 505, 701, 704, 705, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 67 Stat. 477 as amended, 52 Stat. 1057-1058 (21 U.S.C. 351, 352, 353, 355, 371, 374, 375); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

§ 310.201 [Amended]

2. In Subpart C, § 310.201 *Exemption for certain drugs limited by new-drug applications to prescription sale* is amended by removing paragraph (a)(1) and reserving it.

3. Part 343 is added to read as follows:

PART 343—INTERNAL ANALGESIC, ANTIPYRETIC, AND ANTIRHEUMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Labeling

Subpart D—Testing Procedures

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

Subpart A—General Provisions

§ 343.1 Scope.

(a) An over-the-counter analgesic-antipyretic drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part in addition to each of the general conditions established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 343.3 Definitions.

As used in this part:

Analgesic-antipyretic drug. An agent used to alleviate pain and to reduce fever.

Subpart B—Active Ingredients

§ 343.10 Analgesic-antipyretic active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient in § 343.50(d):

(a) Acetaminophen.

(b) *Aspirin ingredients.* (1) Aspirin.

(2) Buffered aspirin. Aspirin identified in paragraph (b)(1) of this section may be buffered with any antacid ingredient(s) identified in § 331.11 of this chapter provided that the finished product contains at least 1.9 milliequivalents of acid-neutralizing capacity per 325 milligrams of aspirin in accordance with § 331.26 of this chapter.

(c) Carbaspirin calcium.

(d) Choline salicylate.

(e) Magnesium salicylate.

(f) Sodium salicylate.

§ 343.20 Permitted combinations of active ingredients.

The following combinations are permitted provided each active ingredient is present within the established dosage limits and the product is labeled in accordance with § 343.60. Combinations containing aspirin must also meet the standards of an acceptable dissolution test, as set forth in § 343.90.

(a) *Combinations of acetaminophen with other analgesic-antipyretic active ingredients.* Acetaminophen identified in § 343.10(a) may be combined with any one ingredient listed below provided that each dose of the product contains 325 to 500 milligrams acetaminophen and the amount of the other ingredient as follows and provided that the product is not labeled for use by children under 12 years of age:

(1) Aspirin 325 to 500 milligrams.

(2) Carbaspirin calcium 414 to 637 milligrams.

(3) Choline salicylate 435 to 669 milligrams.

(4) Magnesium salicylate 377 to 580 milligrams.

(5) Sodium salicylate 325 to 500 milligrams.

(b) *Combinations of analgesic-antipyretic active ingredients with nonanalgesic-nonantipyretic active ingredients*—(1) *Acetaminophen and antacid combinations.* Acetaminophen identified in § 343.10(a) may be combined with any antacid ingredient identified in § 331.11 of this chapter or any combination of antacids permitted in accordance with § 331.10(a) of this chapter provided that the finished product meets all the requirements of § 331.10 of this chapter and bears labeling indications in accordance with § 343.60(b)(2).

(2) *Analgesic-antipyretic and cough-cold combinations.* See § 341.40 of this chapter.

(3) *Aspirin and antacid combinations.* Aspirin identified in § 343.10(b)(1) may be combined with any antacid ingredient identified in § 331.11 of this chapter or any combination of antacids permitted in accordance with § 331.10(a) of this chapter provided that the finished product meets the requirements of § 331.10 of this chapter, is marketed in a form intended for ingestion as a solution, and bears labeling indications in accordance with § 343.60(b)(4).

(4) *Analgesic and diuretic combinations.* Any analgesic identified in § 343.10 or any combination of analgesics identified in § 343.20(a) may be combined with any diuretic identified in § 357.1012 of this chapter provided the product bears labeling indications in accordance with § 357.1060(b) of this chapter.

Subpart C—Labeling

§ 343.50 Labeling of analgesic-antipyretic drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "pain reliever" or "analgesic (pain reliever)." If the product is also labeled to include the indication "to reduce fever," then the statement of identity of the product consists of the established name of the drug, if any, and identifies the product as a "pain reliever-fever reducer" or "analgesic (pain reliever)-antipyretic (fever reducer)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing any ingredient identified in § 343.10.* "For the temporary relief of minor aches and pains" [which may be followed by one or more of the following: ("associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea),") or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)))", ("and for the minor pain from arthritis"), and ("and to reduce fever.")]

(2) *For products labeled only for children 2 years to under 12 years of age.* "For the temporary relief of minor aches and pains" [which may be followed by: ("associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," or "toothache")) and/or ("and to reduce fever.")]

PART 343—INTERNAL ANALGESIC, ANTIPYRETIC, AND ANTIRHEUMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

Subpart A—General Provisions

§ 343.1 Scope.

(a) An over-the-counter analgesic-antipyretic drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part in addition to each of the general conditions established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 343.3 Definitions.

As used in this part:

Analgesic-antipyretic drug. An agent used to alleviate pain and to reduce fever.

Subpart B—Active Ingredients

§ 343.10 Analgesic-antipyretic active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient in § 343.50(d):

(a) Acetaminophen.

(b) *Aspirin ingredients.* (1) Aspirin.

(2) Buffered aspirin. Aspirin identified in paragraph (b)(1) of this section may be buffered with any antacid ingredient(s) identified in § 331.11 of this chapter provided that the finished product contains at least 1.9 milliequivalents of acid-neutralizing capacity per 325 milligrams of aspirin in accordance with § 331.26 of this chapter.

(c) Carbaspirin calcium.

(d) Choline salicylate.

(e) Magnesium salicylate.

(f) Sodium salicylate.

§ 343.20 Permitted combinations of active ingredients.

The following combinations are permitted provided each active ingredient is present within the established dosage limits and the product is labeled in accordance with § 343.60. Combinations containing aspirin must also meet the standards of an acceptable dissolution test, as set forth in § 343.90.

(a) *Combinations of acetaminophen with other analgesic-antipyretic active ingredients.* Acetaminophen identified in § 343.10(a) may be combined with any one ingredient listed below provided that each dose of the product contains 325 to 500 milligrams acetaminophen and the amount of the other ingredient as follows and provided that the product is not labeled for use by children under 12 years of age:

(1) Aspirin 325 to 500 milligrams.

(2) Carbaspirin calcium 414 to 637 milligrams.

(3) Choline salicylate 435 to 669 milligrams.

(4) Magnesium salicylate 377 to 580 milligrams.

(5) Sodium salicylate 325 to 500 milligrams.

(b) *Combinations of analgesic-antipyretic active ingredients with nonanalgesic-nonantipyretic active ingredients*—(1) *Acetaminophen and antacid combinations.* Acetaminophen identified in § 343.10(a) may be combined with any antacid ingredient identified in § 331.11 of this chapter or any combination of antacids permitted in accordance with § 331.10(a) of this chapter provided that the finished product meets all the requirements of § 331.10 of this chapter and bears labeling indications in accordance with § 343.60(b)(2).

(2) *Analgesic-antipyretic and cough-cold combinations.* See § 341.40 of this chapter.

(3) *Aspirin and antacid combinations.* Aspirin identified in § 343.10(b)(1) may be combined with any antacid ingredient identified in § 331.11 of this chapter or any combination of antacids permitted in accordance with § 331.10(a) of this chapter provided that the finished product meets the requirements of § 331.10 of this chapter, is marketed in a form intended for ingestion as a solution, and bears labeling indications in accordance with § 343.60(b)(4).

(4) *Analgesic and diuretic combinations.* Any analgesic identified in § 343.10 or any combination of analgesics identified in § 343.20(a) may be combined with any diuretic identified in § 357.1012 of this chapter provided the product bears labeling indications in accordance with § 357.1060(b) of this chapter.

Subpart C—Labeling

§ 343.50 Labeling of analgesic-antipyretic drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "pain reliever" or "analgesic (pain reliever)." If the product is also labeled to include the indication "to reduce fever," then the statement of identity of the product consists of the established name of the drug, if any, and identifies the product as a "pain reliever-fever reducer" or "analgesic (pain reliever)-antipyretic (fever reducer)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing any ingredient identified in § 343.10.* "For the temporary relief of minor aches and pains" [which may be followed by one or more of the following: ("associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea),") or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea))", ("and for the minor pain from arthritis"), and ("and to reduce fever.")]

(2) *For products labeled only for children 2 years to under 12 years of age.* "For the temporary relief of minor aches and pains" [which may be followed by: ("associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," or "toothache")) and/or ("and to reduce fever.")]

(3) *For products containing acetaminophen as identified in § 343.10(a).* The term "flu" may be added to the indications identified in paragraphs (b) (1) and (2) above.

(4) *Other required statements—(i) For products labeled only for children 2 to under 12 years of age containing any ingredient identified in § 343.10.* (A) The labeling of the product contains, on the principal display panel, either of the following:

(*1*) "Children's *(trade name of product or generic name of ingredient(s))."*

(*2*) *"(Trade name of product or generic name of ingredient(s))* for Children."

(B) The labeling for adults in § 343.50(d) and the statement "Children 2 to under 12 years of age" in § 343.50(d)(3)(ii) are not required.

(ii) *For products labeled only for adults containing any ingredient identified in § 343.10 and any combination identified in § 343.20.* (A) The labeling of the product contains, on the principal display panel, either of the following:

(*1*) "Adult's *(trade name of product or generic name of ingredient(s))."*

(*2*) *"(Trade name of product or generic name of ingredient(s)) for adults."*

(B) The labeling for children in § 343.50(d) and the word "Adults" in § 343.50(d)(3)(i) are not required.

(C) The product should not contain any labeling for children under 12 years of age except the following statement under the heading "Directions," "Children under 12 years of age: consult a doctor."

(c) *Warnings.* The labeling of the product contains the following statements under the heading "Warnings." If applicable, warnings may be combined to eliminate duplicative words or phrases so the resulting warning(s) are clear and understandable.

(1) *For products labeled for adults—*(i) *For products containing any ingredient in § 343.10.* "Do not take this product for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition."

(ii) *For products containing any ingredient in § 343.10 and labeled for the relief of sore throat pain.* "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly."

(iii) *For products containing acetaminophen identified in § 343.10(a).* The following statement must follow the general warning identified in § 330.1(g) of this chapter: "Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms."

(iv) *For products containing aspirin or carbaspirin calcium identified in §§ 343.10 (b) and (c).* (A) "Do not take this product if you are allergic to aspirin or if you have asthma unless directed by a doctor."

(B) The following warning must follow the general warning identified in § 201.63(a) of this chapter: "IMPORTANT: Do not take this product during the last 3 months of pregnancy unless directed by a doctor. Aspirin taken near the time of delivery may "cause bleeding problems in both mother and child."

(C) *For products in a chewable dosage form.* "Do not take this product for at least 7 days after tonsillectomy or oral surgery unless directed by a doctor."

(v) *For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in §§ 343.10 (b), (c), (d), (e), and (f).* (A) "If ringing in the ears or a loss of hearing occurs, consult a doctor before taking any more of this product."

(B) "Do not take this product if you have stomach problems (such as heartburn, upset stomach, or stomach pain) that persist or recur, or if you have ulcers or bleeding problems, unless directed by a doctor."

(C) *"Drug Interaction Precaution.* Do not take this product if you are taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis unless directed by a doctor."

(vi) *For products containing choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (d), (e), and (f).* "Do not take this product if you are allergic to salicylates (including aspirin) unless directed by a doctor."

(vii) *For products containing magnesium salicylate identified in § 343.10(e) in an amount more than 50 milliequivalents of magnesium in the recommended daily dosage.* "Do not take this product if you have kidney disease unless directed by a doctor."

(viii) *For products containing sodium salicylate identified in § 343.10(f)*—(A) *For products containing 0.2 milliequivalent (5 milligrams) or higher of sodium per dosage unit.* The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 milliequivalent (5 milligrams) or higher.

(B) *For products containing more than 5 milliequivalents (125 milligrams) sodium in the maximum recommended daily dosage.* "Do not take this product if you are on a sodium restricted diet unless directed by a doctor."

(2) *For products labeled for children 2 years to under 12 years of age—*(i) *For products containing any ingredient in § 343.10.* "Do not give this product for pain for more than 5 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition."

(ii) *For products containing any ingredient in § 343.10 and labeled for the relief of sore throat pain.* "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly."

(iii) *For products containing acetaminophen identified in § 343.10(a).* The following statement must follow the general warning identified in § 330.1(g) of this chapter: "Prompt medical attention is critical even if you do not notice any signs or symptoms."

(iv) *For products containing aspirin or carbaspirin calcium identified in § 343.10 (b) and (c).* (A) "Do not give this product to children who are allergic to aspirin or who have asthma unless directed by a doctor."

(B) *For products in a chewable dosage form.* "Do not give this product for at least 7 days after tonsillectomy or oral surgery unless directed by a doctor."

(v) *For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (b), (c), (d), (e), and (f).* (A) "If ringing in the ears or a loss of hearing occurs, consult a doctor before giving any more of this product."

(B) "Do not give this product to children who have stomach problems (such as heartburn, upset stomach, or stomach pain) that persist or recur, or who have ulcers or bleeding problems, unless directed by a doctor."

(C) *"Drug Interaction Precaution.* Do not give this product to children who are taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis unless directed by a doctor."

(vi) *For products containing choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (d), (e), and (f).* "Do not give this product to children who are allergic to salicylates (including aspirin) unless directed by a doctor."

(vii) *For products containing magnesium salicylate identified in § 343.10(e) in an amount more than 50 milliequivalents of magnesium in the*

recommended daily dosage. "Do not ...ive this product to children who have ...dney disease unless directed by a ...ctor."

(viii) *For products containing sodium salicylate identified in § 343.10(f)*—(A) *For products containing 0.2 milliequivalent (5 milligrams) or higher of sodium per dosage unit.* The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 milliequivalent (5 milligrams) or higher.

(B) *For products containing more than 5 milliequivalents (125 milligrams) sodium in the maximum recommended daily dosage.* "Do not give this product to children who are on a sodium restricted diet unless directed by a doctor."

(3) *For products labeled both for adults and for children 2 years to under 12 years of age.* The labeling of the product contains the warnings identified in § 343.50(c)(1) except that the warning in § 343.50(c)(1)(i) is replaced with the following: "Do not take this product for pain for more than 10 days (for adults) or 5 days (for children), and do not take for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is ...esent, consult a doctor because these ...d be signs of a serious condition. Do ...ive this product to children for the ... of arthritis unless directed by a ...tor."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions."

(1) *"For products labeled only for children 2 years to under 12 years of age."* The dosage information for children in paragraphs (d) (2), (4), (5), and (6) of this section should be converted to directions that are easily understood by the consumer. For example, the number of 80-milligram, or 81-milligram, or 325-milligram dosage units corresponding to the children's doses in paragraph (d)(2) of this section can be expressed in the labeling as follows:

DIRECTIONS

Age (years)	Number of 80-mg or 81-mg [1] dosage units	Number of 325-mg [1] dosage units
Under 2	Consult a doctor.	Consult a doctor
...der 4	2	½.
...r 6	3	¾.
...9	4	1
...11	4 to 5	1 to 1¼

DIRECTIONS—Continued

Age (years)	Number of 80-mg or 81-mg [1] dosage units	Number of 325-mg [1] dosage units
11 to under 12	4 to 6	1 to 1½.

[1] Dose may be repeated every 4 hours while symptoms persist, up to four times a day or as directed by a doctor.

(2) *For products containing acetaminophen, aspirin, or sodium salicylate identified in § 343.10(a), (b), and (f).* Adults: Oral dosage is 325 to 650 milligrams every 4 hours or 325 to 500 milligrams every 3 hours or 650 to 1,000 milligrams every 6 hours, while symptoms persist, not to exceed 4,000 milligrams in 24 hours, or as directed by a doctor. Children 11 to under 12 years of age: Oral dosage is 320 to 487.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,437.5 milligrams in 24 hours. Children 9 to under 11 years of age: Oral dosage is 320 to 406.3 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,031.5 milligrams in 24 hours. Children 6 to under 9 years of age: Oral dosage is 320 to 325 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,625 milligrams in 24 hours. Children 4 to under 6 years of age: Oral dosage is 240 to 243.8 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,219 milligrams in 24 hours. Children 2 to under 4 years of age: Oral dosage is 160 to 162.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 812.5 milligrams in 24 hours. Children under 2 years: Consult a doctor. The dosage schedules above are followed by "or as directed by a doctor."

(3) *For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10(b), (c), (d), (e), and (f) intended for oral administration as a solid dosage form.* (i) "Adults: Drink a full glass of water with each dose."

(ii) "Children 2 to under 12 years of age: Drink water with each dose."

(4) *For products containing carbaspirin calcium identified in § 343.10(c).* Adults: Oral dosage is 414 to 828 milligrams every 4 hours or 414 to 637 milligrams every 3 hours or 828 to 1,274 milligrams every 6 hours, while symptoms persist, not to exceed 5,096 milligrams in 24 hours. Children 11 to under 12 years of age: Oral dosage is 408.8 to 621 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 3,105 milligrams in 24 hours. Children 9 to under 11 years of age: Oral dosage is 408.8 to 517.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,587.5 milligrams in 24 hours. Children 6 to under 9 years of age: Oral dosage is 408.8 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,070 milligrams in 24 hours. Children 4 to under 6 years of age: Oral dosage is 306.6 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,552.5 milligrams in 24 hours. Children 2 to under 4 years of age: Oral dosage is 204.4 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,035 milligrams in 24 hours. Children under 2 years: Consult a doctor. The dosage schedule above is followed by "or as directed by a doctor."

(5) *For products containing choline salicylate identified in § 343.10(d).* Adults: Oral dosage is 435 to 870 milligrams every 4 hours or 435 to 669 milligrams every 3 hours or 870 to 1,338 milligrams every 6 hours, while symptoms persist, not to exceed 5,352 milligrams in 24 hours. Children 11 to under 12 years of age: Oral dosage is 430 to 652.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 3,262.5 milligrams in 24 hours. Children 9 to under 11 years of age: Oral dosage is 430 to 543.8 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,719 milligrams in 24 hours. Children 6 to under 9 years of age: Oral dosage is 430 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,175 milligrams in 24 hours. Children 4 to under 6 years of age: Oral dosage is 322.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,632.5 milligrams in 24 hours. Children 2 to under 4 years of age: Oral dosage is 215 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,087.5 milligrams in 24 hours. Children under 2 years: Consult a doctor. The dosage schedule above is followed by "or as directed by a doctor."

(6) *For products containing magnesium salicylate, identified in § 343.10(e).* Dosages are based on the tetrahydrate form of magnesium salicylate. Adults: Oral dosage is 377 to 754 milligrams every 4 hours or 377 to 580 milligrams every 3 hours or 754 to 1,160 milligrams every 6 hours, while symptoms persist, not to exceed 4,640 milligrams in 24 hours. Children 11 to under 12 years of age: Oral dosage is 372.4 to 65.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,827.5 milligrams in 24 hours. Children 9 to under 11 years of age: Oral

dosage is 372.4 to 471.3 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,356.5 milligrams in 24 hours. Children 6 to under 9 years of age: Oral dosage is 372.4 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,885 milligrams in 24 hours. Children 4 to under 6 years of age: Oral dosage is 279.3 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,414 milligrams in 24 hours. Children 2 to under 4 years of age: Oral dosage is 186.2 milligrams every 4 hours while symptoms exist, not to exceed 5 doses or 942.5 milligrams in 24 hours. Children under 2 years of age: Consult a doctor. The dosage schedule above is followed by "or as directed by a doctor."

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

(f) *Optional statement. For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (b), (c), (d), (e), and (f).* The labeling may state in a prominent place the following statement: "See your doctor for other uses of" [insert name of ingredient or trade name of product]", but do not use for more than 10 days without consulting your doctor because serious side effects may occur."

§ 343.60 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (b). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For permitted combinations identified in § 343.20(a).* The indications in § 343.50(b)(1) should be used.

(2) *For permitted combinations identified in § 343.20(b)(1).* The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") (which may be followed by: "and upset stomach associated with" (select one of the following, as appropriate: "this symptom" or "these symptoms.")]

(3) *For permitted combinations identified in § 343.20(b)(2).* The indications in § 341.85 of this chapter should be used.

(4) *For permitted combinations identified in § 343.20(b)(3).* The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") [which may be followed by: "and upset stomach associated with" (select one of the following, as appropriate: "this symptom" or "these symptoms")] and "Also may be used for the temporary relief of minor aches and pains alone" [which may be followed by one or more of the following: ("such as associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea)") or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)")]), ("and for the minor pain from arthritis"), and ("and to reduce fever.")]

(5) *For permitted combinations identified in § 343.20(b)(4).* The indications in § 357.1050(b) of this chapter should be used.

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (d). When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

(1) *For products containing permitted combinations identified in § 343.20(a)—*

(i) *When each ingredient is present in the minimum allowable amount.* Adults: Oral dosage is every 4 hours while symptoms persist, not to exceed 6 doses in 24 hours or as directed by a doctor. Children under 12 years of age: Consult a doctor.

(ii) *When either ingredient is present in an amount above the minimum allowable quantity.* Adults: Oral dosage is every 6 hours while symptoms persist, not to exceed 4 doses in 24 hours or as directed by a doctor. Children under 12 years of age: Consult a doctor.

(e) *Optional labeling statements for permitted combinations identified in § 343.20(b)(3).* The labeling may state "Contains buffering ingredients." The labeling may also contain the statement in § 343.50(f).

§ 343.80 Professional labeling.

The labeling of a product provided to health professionals (but not to the general public) may contain the following statements:

(a) *For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (b), (c), (d), (e), and (f) except those buffered with sodium.* "For rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis (degenerative joint disease), ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, and fibrositis."

(b) *For products containing aspirin identified in § 343.10(b) except those buffered with sodium.* The labeling states, under the heading "ASPIRIN FOR TRANSIENT ISCHEMIC ATTACKS," the following:

"Indication:

For reducing the risk of recurrent transient ischemic attacks (TIA's) or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli. There is inadequate evidence that aspirin or buffered aspirin is effective in reducing TIA's in women at the recommended dosage. There is

no evidence that aspirin or buffered aspirin is of benefit in the treatment of completed strokes in men or women.

Clinical Trials:

The indication is supported by the results of a Canadian study (1) in which 585 patients with threatened stroke were followed in a randomized clinical trial for an average of 26 months to determine whether aspirin or sulfinpyrazone, singly or in combination, was superior to placebo in preventing transient ischemic attacks, stroke, or death. The study showed that, although sulfinpyrazone had no statistically significant effect, aspirin reduced the risk of continuing transient ischemic attacks, stroke, or death by 19 percent and reduced the risk of stroke or death by 31 percent. Another aspirin study carried out in the United States with 178 patients, showed a statistically significant number of "favorable outcomes," including reduced transient ischemic attacks, stroke, and death (2).

Precautions:

Patients presenting with signs and symptoms of TIA's should have a complete medical and neurologic evaluation. Consideration should be given to other disorders that resemble TIA's. Attention should be given to risk factors: it is important to evaluate and treat, if appropriate, other diseases associated with TIA's and stroke, such as hypertension and diabetes.

Concurrent administration of absorbable antacids at therapeutic doses may increase the clearance of salicylates in some individuals. The concurrent administration of nonabsorbable antacids may alter the rate of absorption of aspirin, thereby resulting in a decreased acetylsalicylic acid/salicylate ratio in plasma. The clinical significance of these decreases in available aspirin is unknown.

Aspirin at dosages of 1,000 milligrams per day has been associated with small increases in blood pressure, blood urea nitrogen, and serum uric acid levels. It is recommended that patients placed on long-term aspirin treatment be seen at regular intervals to assess changes in these measurements.

Adverse Reactions:

At dosages of 1,000 milligrams or higher of aspirin per day, gastrointestinal side effects include stomach pain, heartburn, nausea and/or vomiting, as well as increased rates of gross gastrointestinal bleeding."

(Other applicable warnings related to the use of aspirin as described in § 343.50(c) may also be included here.)

Dosage and Administration:

Adult oral dosage for men is 1,300 milligrams a day, in divided doses of 650 milligrams twice a day or 325 milligrams four times a day.

References

(1) The Canadian Cooperative Study Group, "A Randomized Trial of Aspirin and Sulfinpyrazone in Threatened Stroke," *New England Journal of Medicine*, 299:53–59, 1978.

(2) Fields, W.S., et al., "Controlled Trial of Aspirin in Cerebral Ischemia " *Stroke* 8:301–316, 1977."

(c) *For products containing aspirin identified in § 343.10(b) or permitted combinations identified in § 343.20(b)(3).* The labeling states, under the heading "ASPIRIN FOR MYOCARDIAL INFARCTION," the following:

"Indication

Aspirin is indicated to reduce the risk of death and/or non-fatal myocardial infarction in patients with a previous infarction or unstable angina pectoris.

Clinical Trials

The indication is supported by the results of six large, randomized multicenter, placebo-controlled studies involving 10,816, predominantly male, post-myocardial infarction (MI) patients and one randomized placebo-controlled study of 1,266 men with unstable angina (1–7). Therapy with aspirin was begun at intervals after the onset of acute MI varying from less than 3 days to more than 5 years and continued for periods of from less than 1 year to 4 years. In the unstable angina study, treatment was started within 1 month after the onset of unstable angina and continued for 12 weeks, and patients with complicating conditions such as congestive heart failure were not included in the study.

Aspirin therapy in MI patients was associated with about a 20-percent reduction in the risk of subsequent death and/or non-fatal reinfarction, a median absolute decrease of 3 percent from the 12- to 22-percent event rates in the placebo groups. In aspirin-treated unstable angina patients the reduction in risk was about 50 percent, a reduction in the event rate of 5 percent from the 10-percent rate in the placebo group over the 12-weeks of the study.

Daily dosage of aspirin in the post-myocardial infarction studies was 300 milligrams in one study and 900 to 1,500 milligrams in 5 studies. A dose of 325 milligrams was used in the study of unstable angina.

Adverse Reactions

Gastrointestinal Reactions

Doses of 1,000 milligrams per day of aspirin caused gastrointestinal symptoms and bleeding that in some cases were clinically significant. In the largest post-infarction study (the Aspirin Myocardial Infarction Study (AMIS) with 4,500 people), the percentage incidences of gastrointestinal symptoms for the aspirin (1,000 milligrams of a standard, solid-tablet formulation) and placebo-treated subjects, respectively, were: stomach pain (14.5 percent; 4.4 percent); heartburn (11.9 percent; 4.8 percent); nausea and/or vomiting (7.6 percent; 2.1 percent); hospitalization for gastrointestinal disorder (4.8 percent; 3.5 percent). In the AMIS and other trials, aspirin-treated patients had increased rates of gross gastrointestinal bleeding. Symptoms and signs of gastrointestinal irritation were not significantly increased in subjects treated for unstable angina with buffered aspirin in solution."

(Other applicable warnings related to the use of aspirin as described in § 343.50(c) may also be included here.)

"Cardiovascular and Biochemical

In the AMIS trial, the dosage of 1,000 milligrams per day of aspirin was associated with small increases in systolic blood pressure (BP) (average 1.5 to 2.1 millimeters) and diastolic BP (0.5 to 0.8 millimeters), depending upon whether maximal or last available readings were used. Blood urea nitrogen and uric acid levels were also increased, but by less than 1.0 milligram percent.

Subjects with marked hypertension or renal insufficiency had been excluded from the trial so that the clinical importance of these observations for such subjects or for any subjects treated over more prolonged periods is not known. It is recommended that patients placed on long-term aspirin treatment, even at doses of 300 milligrams per day, be seen at regular intervals to assess changes in these measurements.

Sodium in Buffered Aspirin for Solution Formulations

One tablet daily of buffered aspirin in solution adds 553 milligrams of sodium to that in the diet and may not be tolerated by patients with active sodium-retaining states such as congestive heart or renal failure. This amount of sodium adds about 30 percent to the 70- to 90-milliequivalents intake suggested as appropriate for dietary treatment of essential hypertension in the "1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (8).

Dosage and Administration

Although most of the studies used dosages exceeding 300 milligrams, 2 trials used only 300 milligrams and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 milligrams or a conventional 325 milligram aspirin dose is a reasonable, routine dose that would minimize gastrointestinal adverse reactions. This use of aspirin applies to both solid, oral dosage forms (buffered and plain aspirin) and buffered aspirin in solution.

References

(1) Elwood, P.C., et al., "A Randomized Controlled Trial of Acetylsalicylic Acid in the Secondary Prevention of Mortality from Myocardial Infarction." *British Medical Journal*, 1:436–440, 1974.

(2) The Coronary Drug Project Research Group, "Aspirin in Coronary Heart Disease," *Journal of Chronic Diseases*, 29:625–642, 1976.

(3) Breddin K., et al., "Secondary Prevention of Myocardial Infarction: A Comparison of Acetylsalicylic Acid, Phenprocoumon or Placebo," *Homeostasis*, 470:263–268, 1979.

(4) Aspirin Myocardial Infarction Study Research Group, "A Randomized, Controlled Trial of Aspirin in Persons Recovered from Myocardial Infarction," *Journal of the American Medical Association*, 243:661–669, 1980.

(5) Elwood, P.C., and P.M. Sweetnam, "Aspirin and Secondary Mortality after Myocardial Infarction," *Lancet*, II:1313–1315, December 22–29, 1979.

(6) The Persantine-Aspirin Reinfarction Study Research Group, "Persantine and Aspirin in Coronary Heart Disease," *Circulation*, 62:449–461, 1980.

(7) Lewis, H.D., et al., "Protective Effects of Aspirin Against Acute Myocardial Infarction and Death in Men with Unstable Angina, Results of a Veterans Administration Cooperative Study," *New England Journal of Medicine*, 309:396–403, 1983.

(8) "1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure," United States Department of Health and Human Services and United States Public Health Service, National Institutes of Health, Publication No. NIH 84–1088, 1984."

Subpart D—Testing Procedures

§ 343.90 Dissolution Testing.

(a) *Acetaminophen and aspirin tablets.* Acetaminophen and aspirin tablets must meet the dissolution standard for acetaminophen and aspirin tablets as contained in U.S.P. XXI at page 14.

(b) *Aspirin capsules.* Aspirin capsules must meet the dissolution standard for aspirin capsules as contained in U.S.P. XXI at page 77.

(c) *Aspirin delayed-release capsules and aspirin delayed-release tablets.* Aspirin delayed-release capsules and aspirin delayed-release tablets must meet the dissolution standard for aspirin delayed-release capsules and aspirin delayed-release tablets as contained in U.S.P. XXI Supplement 3 at pages 1972 and 1973, respectively.

(d) *Aspirin tablets.* Aspirin tablets must meet the dissolution standard for aspirin tablets as contained in U.S.P. XXI Supplement 4 at page 2130.

(e) *Aspirin, alumina, and magnesia tablets.* Aspirin in combination with alumina and magnesia in a tablet dosage form must meet the dissolution standard for aspirin, alumina, and magnesia tablets as contained in U.S.P. XXI Supplement 2 at pages 1812 and 1813.

(f) *Buffered aspirin tablets.* Buffered aspirin tablets must meet the dissolution standard for buffered aspirin tablets as contained in U.S.P. XXI Supplement 4 at page 2131.

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

4. The authority citation for 21 CFR Part 369 continues to read as follows:

Authority: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050–1052 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.10 and 5.11.

§ 369.20 [Amended]

5. In Subpart B, § 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entry for "SALICYLATES, INCLUDING ASPIRIN AND SALICYLAMIDE (EXCEPT METHYL SALICYLATE, EFFERVESCENT SALICYLATE PREPARATIONS, AND PREPARATIONS OF AMINOSALICYLIC ACID AND ITS SALTS)."

§ 369.21 [Amended]

6. In Subpart B, § 369.21 *Drugs; warning and caution statements required by regulations* is amended by removing the entry for "ACETAMINOPHEN (N-ACETYL-*p*-AMINOPHENOL)."

Dated: August 5, 1988.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 88–26157 Filed 11–15–88; 8:15 am]

BILLING CODE 4160-01-M